

**Avoiding Adverse Drug Reactions in Children -
Development of the Liverpool Adverse Drug Reaction
Avoidability Assessment Tool**

Thesis submitted in accordance with the requirements of
the University of Liverpool for the degree of Doctor in
Philosophy

by

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August 2015

Abstract

Adverse drug reactions (ADRs) are common in children. They contribute significantly to patient morbidity, mortality and hospitalisation costs. There is limited data on the avoidability of ADRs in children and wide variation in avoidability rates has been reported. There is currently no standardised method for determining avoidability and many of the established tools are not suitable or designed for use in paediatrics. The aim of this thesis was to develop and test a new avoidability assessment tool that is suitable for use in paediatrics. The stimulus for this work was difficulty using other tools including the one developed by Hallas et al. (1990). Ideally the new tool should also be applicable and generalisable to a variety of other settings. A secondary objective was to identify potential strategies for clinical practice that might reduce the incidence of ADRs. Three key themes for avoidability have been established through a review of existing literature these are: inappropriate or suboptimal prescribing, inadequate monitoring and inadequate patient or parent education.

The development of the LAAT was a multistep process which involved a multidisciplinary team (MDT). Individual and group assessments were conducted and qualitative and quantitative analyses of the assessments were carried out. The LAAT has undergone validity and reliability testing for groups and individuals. The newly validated LAAT was used to assess 249 ADR case reports from a prospective paediatric admissions study by one individual and compared to existing avoidability assessments conducted using the Hallas scale. Assessment of these ADR case reports using the LAAT found that 19.3% were either possibly or definitely avoidable. This was similar to results using the Hallas scale where 22% of the reactions were either possibly or definitely avoidable. Overall percentage exact agreement (%EA) between LAAT and the Hallas scale was 90%; when subcategorised into oncology and non-oncology cases the %EA was found to be 94.2 and 86% respectively. The kappa score between LAAT and Hallas scale assessments

was 0.71 (95% CI 0.60 - 0.82) for all cases, 0.54 (95% CI 0.40 - 0.68) for the oncology cases and 0.73 (95% CI 0.58 - 0.88) for the non-oncology cases. The most common avoidability theme detected in this study was inappropriate or suboptimal prescribing.

Assessing the avoidability of ADRs is a complex process which requires taking into account a number of factors. Strategies to avoid ADRs can be applied at different levels including: patient, ward, departmental institutional, professional, and national. A common theme that emerged from this work was the lack of available guidelines that could be used to assess whether ADRs were avoidable. Where guidelines were available few contained information about ADRs or their prevention. The majority of clinicians relied on their experience and tacit knowledge rather than on guidelines. Some of the ADRs categorised as either possibly or definitely avoidable may have been avoidable with improved prescribing, more frequent monitoring or improved education of patients and/or parents. Other possible prevention strategies include creating an awareness of ADRs in general and their prevention throughout a clinician's training. Improved communication and documentation in patient records is a simple but effective method of ADR reduction.

In summary, we have designed a novel avoidability assessment tool, developed by a multidisciplinary team, and have shown that the new tool is comparable to an existing avoidability tool, can be used by individuals and most importantly is suitable for use in paediatrics or other areas where clinical conditions extend beyond the expertise of individuals. The LAAT refers to guidelines and patient history rather than to abstract concepts such as 'present-day knowledge of good medical practice' and 'effort exceeding the obligatory demands' as per Hallas. Further work to identify potentially avoidable ADRs and strategies to prevent them is needed.

Acknowledgements

I would like to start by sincerely thanking my supervisors Dr Mark Turner, Professor Tony Nunn, Professor Munir Pirmohamed and Dr Jamie Kirkham for their continued support and guidance. I would also like to thank Professor Matthew Peak and Dr Janine Arnott for their expertise and support particularly with the qualitative work in Chapter 4. Thank you to the members of the ADRIC team, Dr Jenny Bellis, Dr Signe Thiesen, Helena Mannix and Jenny Duncan for their contribution to the work in this thesis and their encouragement; particularly, Helena for taking part in the tool development consensus meetings (work carried out in Chapter 2) and to Jenny Duncan for moderating the consensus groups (work carried out in Chapters 3 and 4). A special thank you to all the clinicians who kindly agreed to take part in the studies discussed in Chapters 2, 3 and 4, without which this work would not have been possible. I'm extremely grateful to the ADRIC senior investigators for allowing me to undertake a research degree and to the NIHR for providing funding for the ADRIC Programme. I would also like to thank Barbara Richards and Rebekah Hughes the ADRIC programme administrators for their assistance. Finally, I would like to thank my family and friends for their love and support throughout, particularly my husband Karl, for his patience!

List of Abbreviations

%EA	Percentage exact agreement
%ED	Percentage extreme disagreement
AAT	Avoidability assessment tool
ABCC3	ATP-binding cassette transporter C3
ADE	Adverse drug event
ADR	Adverse drug reaction
ADRIC	Adverse Drug Reactions in Children
ADVISE	Adverse Drug Reactions in Children- International Surveillance & Evaluation
AE	Adverse event
ALL	Acute lymphoblastic leukaemia
APA	Association of Paediatric Anaesthetists
BARDI	Bayesian Adverse Reaction Diagnostic Instrument
BMJ	British Medical Journal
BNF-C	British National Formulary for Children
BPCA	Best Pharmaceuticals for Children Act
CDSS	Clinical decision support systems
CG	Consensus group
CHM	Commission on Human Medicines
COMPT	Catechol-O-methyltransferase
CPD	Continuing professional development
CPPE	Centre for Pharmacy Postgraduate Education
D1/D2/D3	Doctor 1, 2 or 3
DoTS	Dose-relatedness, Timing and Susceptibility
DRP	Drug related problem
EMA	European Medicines Agency
EP	Electronic prescribing
EU	European Union
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernisation Act
FY1	First year foundation
GA	General anaesthetic
GCSF	Granulocyte colony stimulating factors
GFR	Glomerular filtration rate
GS	Gold standard
GWAS	Genome-wide association study
HR	Hazard ratio

IRR	Inter-rater reliability
LAAT	Liverpool Avoidability Assessment Tool
LCAT	Liverpool Causality Assessment Tool
LOS	Length of stay
MA	Marketing authorisation
MDT	Multidisciplinary team
ME	Medication error
MHRA	Medicines and Healthcare Regulatory Agency
N1/N2/N3	Nurse 1, 2 or 3
NGT	Nominal group technique
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
P1/P2/P3	Pharmacist 1, 2 or 3
PD	Pharmacodynamic
PDCO	The Paediatric Committee
PIP	Paediatric investigation plan
PK	Pharmacokinetic
PONV	Post-operative nausea and vomiting
POV	Post-operative vomiting
PREA	Paediatric Research Equity Act
PUMA	Paediatric Use Marketing Authorisation
R&D	Research and Development
RCA	Root cause analysis
RCPCH	Royal College of Paediatrics and Child Health
RCT	Randomised controlled trial
RMP	Risk management plan
SIGN	Scottish Intercollegiate Guidelines Network
SmPC	Summary of Product Characteristics
SPC	Supplementary protection certificate
TPMT	Thiopurine S-methyltransferase
UK	United Kingdom
US	United States
WHO	World Health Organisation
YC	Yellow card
YCS	Yellow card scheme

Publications and presentations arising from work in this thesis

Conference presentations:

Oral presentation:

Work from Chapter 2 was presented at the 54th Annual Meeting European Society for Paediatric Research October 10th-14th, 2013 - Porto, Portugal:

Development of the Liverpool Adverse Drug Reaction Avoidability Assessment Tool

Poster presentations:

Work from Chapter 2 was presented at the Neonatal and Paediatric Pharmacists Group 19th Annual Conference (London, November 2013).

Development of an Adverse Drug Reaction Avoidability Assessment Tool

Abstract published in Arch Dis Child (Bracken et al. 2014a)

Work from Chapter 3 was presented at the 5th Congress of the European Academy of Paediatric Societies EAPS 17–21 October 2014, Barcelona, Spain:

Are Group Assessments Superior To Individual Avoidability Assessments? A Test of The Liverpool Adverse Drug Reaction Avoidability Assessment Tool

Abstract published in Arch Dis Child 2014 (Bracken et al. 2014b)

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Chapter 1 Introduction

1.1 Background

Adverse drug reactions (ADRs) contribute significantly to patient morbidity, mortality and hospitalisation costs. ADRs are a major patient safety issue and they can have significant consequences both for the patient and health care system (Lövborg et al. 2012). A recent systematic review of ADRs in children reported incidences of ADRs in hospitalised children ranging from 0.6 to 16.8% among studies (Smyth et al. 2012). This is similar to the incidence rate in hospitalised adults of 14.7% (Davies et al. 2009). The annual cost of drug related morbidity and mortality has been estimated in the United States at more than \$136 billion and ADRs contribute significantly to these costs (McDonnell et al. 2002). Davies et al. (2009) estimated that in the United Kingdom (UK) ADRs in adults cost the National Health Service (NHS) in excess of £637 million a year; this figure represents an extrapolation from a single NHS hospital to the NHS as a whole. Children are considered to be particularly susceptible to ADRs (Le et al. 2006, Gallagher et al. 2012).

Medicines are commonly prescribed to children, but many have limited data available on their safety and efficacy in children. Prior to the Paediatric Regulation coming into effect a survey conducted by Conroy et al. (2000) in five European hospitals showed that almost half of the medicines prescribed (46%) for use in children had not been tested for use in this specific age group. Over half of the children (67%) in the study received a prescription for an unlicensed or off-label medicine during their inpatient stay (Conroy et al. 2000). The prescribing habits in the five centres varied; but analgesics and bronchodilators were among the top five most frequently prescribed off-label medicines in four out of five centres (Conroy et al. 2000). In 2006 roughly 75% of the 317 centrally licensed medicines were relevant for children but only half (34%) had a paediatric indication (European Medicines Agency 2012). As a result medicines are often prescribed to children off-label

and/or unlicensed. The reported incidence of off-label and unlicensed use of medicines in children ranges from 36 to 100% in paediatric wards (Cuzzolin, Atzei & Fanos 2006). The use of unlicensed and off-label medicines is common, as traditionally clinical trials have not been conducted in children. Some studies have reported the contribution of unlicensed or off-label medicines in the development of ADRs. According to Cuzzolin, Atzei and Fanos (2006) the percentage of off-label or unlicensed medicines involved in ADRs ranged from 23 to 60%.

There is a lack of safety and efficacy data on many medicines used in paediatrics and prescribing in children is often based on extrapolation from clinical trials in adults. The information available to clinicians regarding unlicensed or off-label medicines may not always be as detailed as when prescribing a medicine that is licensed for an approved indication (Langerova, Vrtal & Urbanek 2014). Due to the lack of studies designed to evaluate drug dosing in children, clinicians are often at a disadvantage to make informed therapeutic decisions potentially placing patients at increased risk for adverse drug effects (Kearns 2000). Children are a heterogeneous group and have complex needs. Clinicians may have to take extra steps to consider the potential risks and the potential benefits of treatment.

New legislations were introduced in the European Union (EU) and United States (US) to improve research into paediatric medicines. In 1997 the US initiated legislative changes to encourage more clinical trials in children; the Food and Drug Administration Modernisation Act (FDAMA) was passed (FDA U.S Food and Drug Administration 1997). The FDAMA offered a financial incentive to pharmaceutical companies, an additional six months of market exclusivity if they conducted paediatric trials in line with a Food and Drug Administration (FDA) request. In 2002 the Best Pharmaceuticals for Children Act (BPCA) was implemented. It extended the provision from the 1997 FDAMA, offering an additional 6 months of patent exclusivity for medicines tested for paediatric use. In 2003 the Paediatric Research Equity Act (PREA) was enacted. The introduction of PREA required paediatric assessments of new drug and biologic licensing applications for all new active ingredients (Patrick E. Clarke, Office of Communications 2011). Under PREA the FDA

can request paediatric studies of a drug submitted in a new drug application if the product is likely to be used in a substantial number of paediatric patients, or if the product would provide a meaningful benefit in the paediatric population over existing treatments. This does not delay the availability of drugs for adults. In 2007 the Paediatric Regulation came into effect in the EU. It aimed to improve the availability of medicines for children, to ensure medicines were of high quality, researched and authorised for use in children without subjecting children to unnecessary clinical trials or delaying the approval process of medicines for use in children (European Medicines Agency 2012). Following this the Paediatric Committee (PDCO) was established to assess paediatric investigation plans (PIPs), waivers and deferrals (European Medicines Agency 2012). The Paediatric Regulation also introduced a Paediatric-Use Marketing Authorisation (PUMA) for medicines exclusively used in paediatrics which are not protected by a patent or a supplementary protection certificate (SPC) (European Medicines Agency 2011b). These legislative changes have resulted in an increase in the number of paediatric trials (Joseph, Craig & Caldwell 2015). A report to the European Commission (EC) published in 2012 by the EMA outlined the experience gained as a result of the Paediatric Regulation (European Medicines Agency 2012). By 2011, the European Medicines Agency (EMA) and the PDCO had agreed more than 600 PIPs and the number of clinical trials in children has increased to approximately 10%. Also, as a result of the Paediatric Regulation more information on the use of medicines in children has resulted in updates to Summaries of Product Characteristics (SmPCs) (European Medicines Agency 2013). Despite these advances ADRs in children remain under-studied.

The Adverse Drug Reactions in Children (ADRIC) programme was funded by the National Institute of Health Research (NIHR) to conduct research into ADRs in children. It was a five year programme which consisted of a series of studies investigating ADRs including an admissions study and an inpatient study. The ADRIC admissions study was a prospective observational study carried out over a one year period which examined ADRs causing admission to hospital (Gallagher et al. 2012). The ADRIC inpatient study was a prospective observational cohort study which was

carried out over a one year period and examined ADRs occurring in hospital (Thiesen et al. 2013). A series of qualitative studies described the experiences of parents whose children had experienced an ADR, clinicians' experience of ADRs and developing communication strategies and information leaflets about ADRs for parents (Arnott et al. 2012, Smyth et al. 2014). A systematic review was also conducted. During the course of the programme, it was found that none of the commonly used tools to assess causality and avoidability of ADRs were sufficiently reliable to be used in these studies (the reliability issues of commonly used causality and avoidability tools are discussed in more detail later in this chapter in Section 1.8 (Evaluation of adverse drug reactions)). This led to the development and validation of new assessment tools - the Liverpool causality assessment tool (LCAT) (Gallagher et al. 2011b) and the Liverpool avoidability assessment tool (LAAT) (Bracken et al. 2014a).

This chapter will firstly look at how ADRs are defined and classified, the incidence of ADRs in children, risk factors and characterisation. It will go on to focus on the avoidability of ADRs; the methodology of assessing avoidability and finally, it will review previous studies which have examined the avoidability of ADRs in children.

1.1 Definitions

There is an issue regarding terminology used in the area of pharmacovigilance and this can make the comparison of studies difficult (Hakkarainen et al. 2012a). Aronson and Ferner (2005) produced a paper on the terminology used in drug safety in an attempt to clarify this complex area. Consistent terminology is essential. A clear definition of adverse drug reactions is needed so that data on ADRs can be consistently reported and reliably interpreted.

There are a number of definitions of ADRs. The two definitions below have been widely used in ADR studies. The World Health Organisation (WHO) definition (1972) of an adverse drug reaction has been in existence for over 40 years:

'A response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function'.

This definition is widely accepted. However, the use of the word 'noxious' has been criticised in the past for being vague. It raises the question; does it include all adverse reactions irrespective of how minor they are? In which case it may lead to the reporting of large numbers of common minor ADRs to the regulatory bodies (Edwards, Aronson 2000)

This led to Edwards and Aronson (2000) proposing their own definition of an ADR:

'An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen or withdrawal of the product'.

The two definitions above do not include responses or reactions resulting from drug errors or from poisoning (deliberate or accidental). In 2010 the European Parliament and Council of Ministers adopted a new directive on the community code relating to medicinal products for human use. The definition of the term 'adverse reaction' was updated to include noxious and unintended effects resulting from medication errors (MEs) and use outside the marketing authorisation (MA), including misuse and abuse of the medicinal product in addition to the effects resulting from the authorised use of a medicine (The European Parliament and the Council of the European Union 2010). New pharmacovigilance legislation came into effect in July 2012 (The European Parliament and the Council of the European Union 2012).

EU definition of ADR

Definition of Adverse Reaction Directive 2001/83/EC - Article 1(11)

Prior to July 2012: *'A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis,*

diagnosis or therapy of disease or for the restoration, correction or modification of physiological function’.

After July 2012: *‘A response to a medicinal product which is noxious and unintended’.*

Following the EU Directive 2010/84/EU1 that came into force in July 2012, the MHRA define the term ADR as,

‘A response to a medicinal product that is noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse, off-label use and abuse of the medicinal product.’

The definitions and terms used depend on the country of origin of the article. There is overlap between the terms. For example all ADRs are adverse events (AEs), but not all AEs are ADRs. An adverse event is any undesirable event experienced by a patient whilst taking a medicine, regardless of whether or not the medicine is suspected to be related to the event (Aronson, Ferner 2005). Some studies have included ADRs alongside drug errors under the term ‘adverse drug event’ (Bates et al. 1999). The revised definitions of ADRs outlined above now also include drug errors.

An adverse drug event (ADE) is defined as *‘an injury resulting from medical intervention related to a drug’* (Bates DW, Cullen DJ, Laird N, et al 1995). The definition was intended to encompass harms that arise from medication errors in addition to ADRs (Aronson 2011).

The WHO define an adverse drug event as *‘Any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment’* (World Health Organisation 2002).

Aronson and Ferner (2005) stated that the term ‘adverse drug event’ could be confusing depending on the usage of it. The term ADE includes harms arising from medication errors and ADRs. If the term were confined to this context, there would

be no problem, the problems arise from its wider use. They also criticised the above definition for being unclear particularly the use of the words “injury” and “medical” (Aronson, Ferner 2005).

The Edwards and Aronson (2000) definition of an ADR is the one used in this thesis. It excludes prescribing errors, administration errors and intentional drug overdoses. The use of the word ‘appreciably’ rules out trivial effects but includes clinically relevant ADRs that the patient detects (Edwards, Aronson 2000). This definition has been used in several studies since its publication; it was the definition used in the ADRIC programme and is the one used in this thesis.

1.3 Adverse drug reaction classification by mechanism

ADRs were formally classified as type A and type B by Rawlins and Thompson (1977). Type A reactions - dose dependent and predictable from the known pharmacology of the drug; and type B reactions - not dose dependent and unpredictable in nature. This classification is simple and has been widely used in the literature. However, not all ADRs can be classified using this system. It has been gradually extended to include type C - dose and time-related, type D - time-related, type E - withdrawal and type F - unexpected failure of therapy. These changes have eliminated some of the issues with the system but have also introduced others (Aronson, Ferner 2003, Aronson, Ferner 2005). They suggested there is overlap between some of the categories. They gave the example of category F (failure) which is an outcome rather than a mechanistic category and could therefore arise from reactions in some of the other categories. They also criticised the fact that dose relatedness had not been considered for the additional categories, whilst Type A and Type B had been classified as dose related or not dose related (Aronson, Ferner 2005).

Aronson and Ferner (2003) proposed an alternative classification system Dose-time-susceptibility (DoTS): which is based on dose-relatedness, timing and patient susceptibility. DoTS is a ‘three dimensional approach’ that considers not only the properties of the medicine implicated in the ADR but also the characteristics of the

reaction and of the individual who experienced the reaction. They describe how dose-relatedness is actually relevant to all reactions inclusive of immunological reactions although it is traditionally thought of in the context of non-immunological reactions. They give examples of dose-dependent immunological reactions including the immunogenic response to hepatitis B vaccine and type IV hypersensitivity skin reactions. They suggest dividing ADRs into those that occur at supratherapeutic doses (toxic effects), at standard therapeutic doses (collateral effects) or at subtherapeutic doses in susceptible patients (hypersusceptibility reactions). The concept of timing takes into consideration when the reaction becomes apparent in relation to when the dose was given and a reaction can be classified as either rapid, first dose, early, intermediate, late or delayed. Finally, the risk of an ADR differs among the population. Susceptibility specifically relates to the patient and is dependent on a number of factors including; genetic variation, age, sex, physiological variation, exogenous factors, and disease (Aronson and Ferner, 2003). This system allows an ADR to be profiled and can perhaps improve drug development and patient care (Cox 2008, Aronson, Ferner 2003).

Ferner and Aronson (2010a) proposed a mechanistic adverse effect classification system (EIDOS) which considers five factors and complements the DoTS system. The five elements considered are: an extrinsic chemical species (E) initiates the effect; it interacts with an intrinsic chemical species (I). In order for the interaction to occur the two species must be co-distributed (D) in the body and this interaction produces an outcome (O) the adverse effect which leads to sequela (S) the adverse drug reaction (Aronson, Ferner 2010).

Example of a classification using the EIDOS system (Ferner, Aronson 2010a):

- Extrinsic species (E) - the chemical species that initiates the effect for example glucocorticoid
- Intrinsic species (I) - the chemical species that it affects; calcium homeostasis, osteoblasts
- Distribution (D) - sites of calcium transport, bone
- Outcome (O) - Atrophy: osteoporosis
- Sequelae (S) - Fracture

However, the Rawlins and Thomson (1977) classification is still widely used in ADR studies today perhaps due to its simplicity. It was the one used in the ADRIC studies and in this thesis.

1.4 Changing pharmacology and ADRs in children

The continuous development during childhood presents a challenge to developing, prescribing and administering age appropriate medicines. The paediatric population is very diverse ranging from pre-term neonates to adolescents. Infants and children undergo significant developmental changes over relatively short time periods which have dramatic effect on pharmacokinetics and pharmacodynamics. The most dramatic pharmacokinetic changes take place in the first year of life (Kearns 2000). Challenges include the production of appropriate formulations and the determination of appropriate dosing regimens. It is vital to appreciate that children cannot be viewed simply as small adults (Kearns 2000). It is not always possible to translate what is known about medicine use in adults into recommendations for medicine use in children. According to Mulla (2010) understanding the pharmacokinetic (PK)/pharmacodynamic (PD) relationship is important for clinical practice, particularly where factors such as age, genotype, co-morbidities and co-medications can affect the nature of this relationship.

Children are not only different from adults but differ within their own age groups as they develop. Pharmacokinetics of drugs in children may differ from adults for several reasons: variability due to age, body composition, functionality of liver and kidneys and maturation of enzymatic systems (Cella et al. 2009). Developmental changes in children affect drug disposition. Examples of this include differences in gastric pH and gastric emptying, changes in circulating plasma proteins, increased or decreased expression of the enzymes involved in drug metabolism and differences in glomerular filtration rate (GFR). These changes can affect the absorption, distribution, metabolism and elimination of drugs in children (Becker, Leeder 2010, Kearns 2000).

During the neonatal period intragastric pH is higher (>4), changes in intraluminal pH can directly affect drug dissolution and has an impact on both drug stability and the degree of ionisation thus affecting the amount of drug available for absorption. Hence oral administration of acid labile compounds such as penicillin G have a higher bioavailability in neonates compared to older infants and children because of the relatively high gastric pH in neonates (Kearns et al. 2003). The gastric pH gradually declines after birth and hence the rate of penicillin degradation in the stomach increases, leading to a reduction in drug absorption. Conversely, drugs that are weak acids such as phenobarbital, may require higher oral doses in neonates than in older infants or children to achieve therapeutic plasma levels (Kearns et al. 2003, Kearns 2000, Samardzic, Allegaert & Bajcetic 2015).

Neonates have a thinner stratum corneum which can lead to an increased rate of absorption of a drug through the skin (Samardzic, Allegaert & Bajcetic 2015). The ratio of total body surface area to body mass in infants and young children is far greater than that in adults hence children are potentially exposed to higher levels for topically applied drugs; for example topical corticosteroids and therefore may be exposed to toxic effects (Kearns et al. 2003).

Renal function needs to be considered particularly when using medicines which are renally cleared. The GFR increases rapidly during the first two weeks of life and then rises steadily reaching adult values at between 8 and 12 months of age; the GFR is reduced in pre-term neonates (Kearns et al. 2003). Neonates and young infants have a decreased level of active tubular secretion for the first 12 months. Adult values are achieved by the age of two (Samardzic, Allegaert & Bajcetic 2015). Developmental changes in renal function can greatly affect the plasma clearance of renally excreted medicines and hence need to be considered when prescribing drugs which are predominantly cleared by the kidneys. For example, aminoglycoside dosing regimens need to be adjusted to account for the ontogeny of renal function. Neonates and young infants require an increased dosage interval and/or reduced maintenance dose for a three month period (Samardzic, Allegaert & Bajcetic 2015).

Neonates and young infants have reduced hepatic metabolism of many drugs and subsequently may require increase in dosage interval to account for the increased half-life (Samardzic, Allegaert & Bajcetic 2015). Drugs metabolised in the liver have shown an age-dependent increase in plasma clearance in children under the age of ten years compared with adults which requires higher weight-based dose requirements (Kearns et al. 2003). According to Samardzic, Allegaert and Bajcetic (2015) children aged one to six have an apparent increased level of certain enzymes over adult values. This leads to increased clearance and a decreased half-life resulting in higher dose requirements for certain medicines.

The majority of age specific dosing requirements are based on the known influence of ontogeny on the disposition of drugs (Kearns et al. 2003). For specific drugs there are dramatic differences in the dose and the dosing interval used in children and those used in adults for example certain antibiotics including, gentamicin, ceftazidime and clindamycin all require higher doses on a milligram per kilo basis in neonates, infants and children compared to adults (Kearns et al. 2003). For example aminoglycoside antibiotics require a higher dose due to the distribution volume but they also require an extended dosing interval as the lower rate of clearance requires an extended interval in order to reach a safe trough level. Aminoglycoside clearance reflects GFR and neonatal clearance is reported to be between 1-5% of adult clearance (Allegaert, Langhendries & van den Anker 2013).

Developmental changes are also present in the drug metabolising enzymes which highlight the need for age-appropriate dosage regimens. The expression of phase 1 enzymes (primarily oxidation) changes during development, for example the cytochrome P-450 enzymes. CYP3A7 is the predominant form in foetal liver. It peaks shortly after birth and declines rapidly to almost undetectable levels in adults. Within hours after birth CYP2E1 activity rises and CYP2D6 becomes detectable thereafter. CYP1A2 is the last to appear between one and three months of age. Two medicines commonly prescribed for neonates caffeine and theophylline are both substrates for CYP1A2. In infants over four months of age the clearance of caffeine

from plasma primarily reflects demethylation activity by CYP1A2 (Kearns et al. 2003).

In a paper on the identification of genomic and developmental causes of ADRs in children Becker and Leeder (2010) concluded that a vital first step is the recognition and characterisation of the differences between children and adults so we can systematically approach personalised therapeutics in children. An understanding of developmental changes in drug disposition informs appropriate dosing regimens but also contributes to an explanation of why children's susceptibility to ADRs may vary.

Clinical experience has shown that children differ from adults in terms of risk for particular ADRs for example; delayed maturation of drug metabolising enzymes may be a particular problem in newborns and contribute to concentration dependent drug toxicities. An example of this is cardiovascular collapse due to accumulation of chloramphenicol (parent compound) associated with delayed maturation of glucuronidation. Drug clearance pathways undergo vast changes throughout development; at birth the activity of many enzymes involved in biotransformation are limited or absent which may increase susceptibility to concentration dependent drug toxicity (Becker, Leeder 2010).

Hepatotoxicity associated with sodium valproate (valproic acid) has been reported as more common in children under six. It has been suggested that young children have an increased risk due to their abnormal metabolism of valproic acid (Star, Edwards & Choonara 2014). Epidemiological studies have shown that the risk of fatal hepatotoxicity is highest in children under two receiving polytherapy (Becker, Leeder 2010).

Codeine is metabolised in the liver via both Phase I and Phase II pathways. Codeine is de-methylated by the enzyme CYP2D6 to produce morphine. Codeine metabolism by CYP2D6 typically only accounts for 5% of the dose; further metabolism is via glucuronidation (Rieder, Carleton 2014). Koren et al. (2006) described the risk of opioid toxicity in breastfed infants. They outlined details of a case of a breastfed

baby who died as a result of opioid toxicity. The mother was an ultra-rapid metaboliser for CYP2D6 who metabolized significantly more codeine to morphine than expected which resulted in high concentrations of morphine in the blood (Koren et al. 2006). CYP2D6 has been recognized as a polymorphic enzyme for some time. There are three phenotypes: extensive metabolisers, poor metabolisers and ultra-rapid metabolisers. These polymorphisms show variable expression in different populations. The case of codeine has highlighted the importance of pharmacogenomics for safe and effective drug therapy (Rieder, Carleton 2014).

The EMA and the MHRA have made changes to the guidance on the use of codeine in children for both pain relief and use in the treatment of coughs and colds. The latest guidance from the MHRA on use of codeine on pain relief is that it should only be used to relieve acute moderate pain in children over 12 and only if pain cannot be relieved by alternatives (paracetamol or ibuprofen) alone. The risk of serious and life-threatening ADRs has been highlighted following reports of serious and fatal respiratory depression in children with obstructive sleep apnoea who received codeine after tonsillectomy and/or adenoidectomy. As a result codeine is now contraindicated in all children younger than 18 years who undergo these procedures for obstructive sleep apnoea. Some of the children who suffered severe ADRs had evidence of being ultra-rapid metabolisers of codeine. In these patients, codeine is converted into morphine in the body at a faster rate than normal. This results in high levels of morphine in the blood that can cause toxic effects such as respiratory depression.

There are many genetic variations of CYP2D6, which affect the extent of this conversion in individuals. The review also concluded that codeine is not suitable for all patients known to be CYP2D6 ultra-rapid metabolisers and that codeine should not be used by breastfeeding mothers due to the risk (Medicines and Healthcare Products Regulatory Agency 2013). In 2010 the UK Commission on Human Medicines advised that over-the-counter liquid medicines that contain codeine should not be used for cough suppression in children under 18. A European review has been conducted of the benefits and risks of using codeine to treat cough and

cold symptoms in children. Although impact of age on codeine metabolism is not fully understood, current evidence suggests children under 12 are at a higher risk of serious side effects than children over 12 (Medicines and Healthcare Products Regulatory Agency 2015).

1.5 Pharmacovigilance – detection and monitoring of adverse drug reactions

Pharmacovigilance is defined as *‘the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem’* (World Health Organisation 2004a).

Following the thalidomide disaster in 1961 international efforts were initiated to address drug safety. The WHO established a pharmacovigilance programme in response to the thalidomide tragedy. Legislation regarding pre-marketing efficacy and safety data for medicines was introduced in the UK with the 1968 Medicines Act. Before a medicine is marketed, any experience of its safety and efficacy is limited to its use in clinical trials. A medicine will only have been tested in a relatively small number of patients for a limited time period. Also, the conditions under which patients and medicines are studied in clinical trials do not necessarily reflect the way the medicines are used in hospitals or general practice once they are marketed. Some ADRs may not be seen until a very large number of people have received the medicine. Therefore it is vital that the safety of all medicines is monitored throughout their marketed life. Effective pharmacovigilance post-marketing helps to develop a full drug-safety profile for medicines.

A formal system to monitor the adverse effects of medicines was set up in the UK in 1964. The Yellow Card Scheme (YCS) collects spontaneous reports of ADRs; it is run by the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Commission on Human Medicines (CHM) (MHRA 2013). It has evolved over the years and it recently celebrated its 50th anniversary. Initially only doctors were allowed to report ADRs but it was later expanded to include pharmacists, nurses

and other healthcare professionals and in 2008 it was extended to allow patients to report ADRs. It receives about 25,000 reports of possible side effects each year. Since the YCS was set up in 1964, over 600,000 UK Yellow Cards have been received. It began as a paper based reporting system and in 2002 the introduction of the yellow card (YC) website saw the inclusion of an electronic YC reporting form (MHRA 2013). The scheme has helped to identify numerous important safety issues. There have been many successes with the YCS which have led to changes to SmPCs, changes to the legal status of a medicine, for example, from over-the-counter to prescription only; domperidone is a recent example of this and withdrawal of the medicine in rare cases where, the risks of a medicine are found to outweigh the benefits (MHRA 2014a).

The MHRA no longer requires all suspected adverse drug reactions (ADRs) in children and adolescents to be reported. This change was made in response to feedback that mandatory reporting of all suspected ADRs in children was impractical and deterred reporting. The advice for reporting adverse reactions is now the same for adults and children. The scheme asks that all suspected ADRs to Black triangle drugs (▼) are reported and for established drugs and vaccines all serious ADRs are reported. The aim was to encourage reporting (MHRA 2014b).

The system is hindered by under-reporting. A systematic review of 37 studies from twelve countries on under-reporting of ADRs estimated its incidence to be between 6 and 100% with a median under-reporting rate of 94% (Hazell, Shakir 2006). Some of the reasons for under-reporting include lack of time, different care priorities, uncertainty about the medicine causing the ADR and difficulty accessing reporting forms (Hazell, Shakir 2006). Reminding clinicians to report suspected ADRs can improve reporting rates.

In July 2012, new pharmacovigilance legislation came into effect across the European Union (EU) (The European Parliament and the Council of the European Union 2010), including centralised reporting by industry of ADRs to the EudraVigilance database at the European Medicines Agency (EMA) and the inclusion

of reports from patients as valid, reportable ADRs. Since July 2012, drug companies in the EU have been required to submit a risk management plan (RMP) at the time of application for a MA for new medicinal products (European Medicines Agency 2014). The RMP includes information on the safety profile of the medicine, how risks will be minimised or prevented, any studies planned to find additional information about the safety profile and identifies potential risk factors and how they should be managed. The introduction of RMPs is intended to address the deficit of information regarding safety available at the time of MA. It is recognised that at the time of authorisation, information on the safety of a medicine can be limited due to a number of contributing factors including the relatively small numbers of people involved in clinical trials compared with the intended treatment population. Also there is often a restricted population in terms of age, gender and ethnicity (European Medicines Agency 2014).

1.6 Incidence of adverse drug reactions in children

There have been four main reviews in this area to date and they are discussed here in more detail. Firstly, a systematic review and meta-analysis published in 2001 which included seventeen prospective studies found the overall incidence of ADRs in hospitalised children to be 9.53% (95% CI 6.81, 12.26). The overall rate of admissions due to ADRs was 2.09% (95% CI 1.02, 3.77) and the overall incidence of ADRs in outpatients was 1.46% (95% CI 0.7, 3.03). The reported ADR incidence in hospitalised children ranged from 4.37% to 16.78% among the different studies (9/17) (Impicciatore et al. 2001). The review aimed to explore the usefulness of data derived from observational studies in defining and preventing the risk of pharmacological interventions in children. The review found that polypharmacy was a potential risk factor of ADRs. There was substantial variability in the reported incidences of ADRs which the authors stated was only partly explained by the different number of drugs. The lack of consistent reporting of other variable such as patient age, diagnosis and prescription patterns meant they could not be considered in the analysis.

A review conducted by Clavenna and Bonati (2009) aimed to assess the incidence of ADRs in children and examine safety alerts issued by international drug regulatory agencies since 2001. The review included eight prospective studies published between 2001 and 2007. The estimated the incidence of ADRs at 10.9% (95% CI 4.8, 17.0) in hospitalised children, 1.8% (95% CI 0.4, 3.2) causing admission and 1% (95% CI 0.3, 1.7) in outpatients. The review by Aagaard, Christensen and Hansen (2010) included 33 studies which looked at ADRs in general paediatric populations. The average incidence rate of ADRs in inpatients was 42%, the figure for ADRs causing admission was 9% and for outpatients it was 14%. The review also provided information on the methods and reports types.

However Smyth et al. (2012) stated that there were a number of limitations with the three previous reviews. Firstly, the reviews were conducted using a limited number of keywords and were limited to two electronic databases MEDLINE and EMBASE this may have resulted in the exclusion of relevant studies. Two of the reviews excluded studies that included ADEs as well as ADRs (Aagaard, Christensen & Hansen 2010, Clavenna, Bonati 2009).

The most recent of these systematic reviews was published by Smyth et al. (2012). It aimed to provide a more comprehensive assessment of ADRs in children and to gain an understanding of how ADRs are detected, assessed and avoided. The review included data from 102 studies and was the largest review of ADRs in children to date, although incidence data was not reported by all studies. The incidence rate of ADRs causing admission to hospital ranged from 0.4% to 10.3% with a pooled estimate of 2.9% (95% CI 2.6%, 3.1%) and the incidence of ADRs in hospitalised children ranged from 0.6 to 16.8%. There is wide variation in the incidence of ADRs; Smyth et al. (2012) suggested this may be due the differences between studies such as study duration, population characteristics and clinical setting. Also, the absence of clear definitions in some studies may have affected the results as not all studies provided a definition of the term 'adverse drug reactions' and it was not always clear if their definition of ADRs included prescribing or medication errors (Smyth et al. 2012).

The incidence of ADRs causing admission in the ADRIC study was 2.9% (95% CI 2.5, 3.3); with 240/8345 admissions thought to be related to an ADR (Gallagher et al. 2012). The study by Gallagher et al. (2012) is the largest of its kind in children and the only study to provide information regarding causality, severity, type of reaction, risk factors and avoidability. The ADRIC inpatient study reported an incidence rate of 17.7% in 6,601 admissions (Thiesen et al. 2013). It is the largest study to date; it characterised ADRs in terms of their type, causality and severity. It also identified risk factors which are discussed in more detail below.

1.7 Risk factors for adverse drug reactions

Children are thought to have a higher risk of developing ADRs than adults due to their physiology and their ability to handle medicines. Previously reported risk factors for ADRs in children include gender, number of medicines, use of unlicensed or off-label medicines and age. Polypharmacy is an established risk factor; previous studies have shown that in both children and adults there is an increased risk of developing an ADR. Patients with five or more medicines prescribed had the highest risk of developing an ADR (Rashed et al. 2011). A study in adults by Zopf et al. (2008) found polypharmacy to be a risk factor (Zopf et al. 2008). Rational prescribing and minimising the number of medicines prescribed can potentially help to avoid ADRs.

It has been reported that older children are more at risk of ADRs than their younger counterparts (Gallagher et al. 2012, Rashed et al. 2011, Thiesen et al. 2013) which is perhaps the opposite of what might be expected. With the changing physiology and differences in handling of drugs among the different age groups it may have been reasonable to expect younger children to be more at risk. Rashed et al. (2011) stated that the question remains whether the incidence is higher in older children because more high risk drugs are given to older children? Thiesen et al. (2013) have suggested that perhaps the difference may be due to lack of detection and underreporting in younger children as it can be difficult to distinguish ADRs from

common clinical issues in children for example loose stools and vomiting may be more 'normal' in younger children thus making it difficult to establish causality.

A study by Turner et al. (1999) of 1046 inpatients which examined ADRs associated with unlicensed and off-label medicines found the overall incidence of ADRs to be 11%. 6% of these were due to unlicensed or off-label medicines. They found an association between the number of medicines administered and the risk of an ADR. The study also showed a potential higher risk of an ADR with unlicensed or off-label medicines and suggested further studies were needed to determine the risk (Turner et al. 1999). Work conducted by Bellis et al. (2013) found that unlicensed and off-label prescribing was a risk factor for ADRs as was the number of medicines irrespective of licensing status (Bellis et al. 2013).

The ADRIC admissions study, a large prospective study of 8345 admissions, reported an ADR incidence of 2.9%. The medicine types most frequently implicated in ADRs were antineoplastic agents, non-steroidal anti-inflammatory drugs, vaccines, immunosuppressants and corticosteroids. Risk factors identified in the admissions study were number of medicines, oncological treatment and increasing age (Gallagher et al. 2012). The ADRIC inpatients study included a total of 5118 children in 6601 admissions. They reported the ADR incidence rate of 17.7% with opioid analgesics and drugs used in general anaesthesia accounting for over 50% of the medicines implicated in ADRs (Thiesen et al. 2013). Risk factors identified were number of medicines, oncological treatment, increasing age and receipt of a general anaesthetic. Thiesen et al. (2013) found children who had received a general anaesthetic (GA) were six times more likely to develop an ADR (hazard ratio (HR) 6.40; 95% CI 5.30-7.70). The risk of experiencing an ADR in patients receiving a GA has not been assessed previously. Most previous paediatric inpatient studies were carried out in general paediatric settings in which only a small number of patients will have undergone GAs. Rashed et al. (2012) reported that anaesthetic drugs were among the drugs most commonly implicated in ADRs, but accounted for only 1% of all prescriptions in their study which was conducted on general medical wards.

The ADVISE study (Adverse Drug Reactions in Children- International Surveillance and Evaluation) was a prospective multicentre cohort study conducted on paediatric general medical wards in five different countries (two European and three non-European sites). ADRs were identified by intensive chart review and were evaluated by the research team, which included at least one clinical pharmacist and one paediatrician and/or paediatric pharmacologist. They assessed causality, avoidability, severity and seriousness using standardised criteria. They used a system introduced by Schumock and Thornton (1992) to assess avoidability. They included a total of 1253 patients in their study and of these, 1115 (89%) received prescribed medicines during their stay. They used the WHO (1972) definition of an ADR. They identified a total of 328 ADRs and reported an overall ADR incidence rate of 16.7% (95% CI 14.5, 19.0) (Rashed et al. 2011). They investigated the following risk factors: age, gender, number of medicines (high and low risk drugs), length of stay and diagnoses. They concluded that number of medicines, older age, presence of certain diseases, disorders or conditions were all independent predictors of ADRs. They found that gender did not appear to have the same effect on ADR epidemiology as in adults. They defined high-risk drugs as analgesics, antiepileptics, antibacterials and antimycotics for systemic use, corticosteroids for systemic use and immunosuppressants. All other medicines were classified as low risk for the study purposes. They found that the use of five or more low risk drugs or three or more high risk drugs were strong predictors of ADRs.

1.8 Evaluation of adverse drug reactions

This review will focus on the three main areas of ADR assessment, causality, severity and avoidability.

1.8.1 Causality assessment

Causality assessment examines the relationship between the ADR and the suspected medicine and the likelihood that the medicine caused the ADR. In order to conduct this assessment several questions must be answered:

- 1 Are there previous reports of the ADR?
- 2 Did it appear after the suspected medicine was administered?
- 3 Did it resolve when the medicine was stopped?
- 4 Could there be another plausible explanation for it e.g. underlying disease?
- 5 If the medicine was given again, did it reoccur?
- 6 Was there any objective evidence of the ADR?
- 7 Did the patient have a similar reaction in the past to the same or any similar medicines?

There are numerous methods for assessing the causality of ADRs. A recent systematic review found 34 different methods and acknowledged that there is currently no 'gold standard' method (Agbabiaka, Savovic & Ernst 2008). The methods fall into three categories: expert judgement/global introspection, algorithms and probabilistic methods (Bayesian approaches). The assessment methods however different share some common features. Algorithms were the most common method found in the review.

1.8.2 Expert judgement/global introspection

This method of causality determination is based on the personal judgement of each ADR report by the investigator, following careful consideration of the available data. It involves the application of clinical opinion. This can be carried out by a single investigator or by a group, who then compare their evaluations to arrive at a consensus opinion. Although this method is widely used, several reports have shown that expert judgement is not a reliable method for causality assessments (Agbabiaka, Savovic & Ernst 2008). Due to the subjectivity of this method there is no guarantee of a consistent approach. Despite these issues it remains popular for ADR assessments, perhaps because it is straightforward.

1.8.3 Algorithms

Algorithms provide a systematic approach for ADR assessment using structured and standardised methods. Several algorithms have been developed to assess the causality of ADRs. Three of these algorithms, Karch and Lasagna (1977), Kramer et al. (1979) and Naranjo et al. (1981) are discussed.

Karch and Lasagna (1977) developed an algorithm based around three decision tables intended to assess potential ADRs, the certainty of the link between the event and the agent and evaluate the underlying causes of the identified adverse events. If the possibility of a link was established, it was categorised as definite, probable, possible, conditional or unrelated. These criteria include knowledge of the reaction, the temporal relationship, presence of known alternative causes, information about dechallenge and rechallenge. The algorithm still requires the investigator to make certain judgements therefore, results may not always be reproducible.

Kramer et al. (1979) expanded on the work of Karch and Lasagna (1977) and produced a set of diagnostic criteria providing specific rules for the assessment of ADRs. The algorithm is comprised of six axes of decision tables, each with a scoring system. The axes are as follows: previous general experience with the drug, alternative etiologic candidates, timing of events, drug levels and evidence of overdose, dechallenge and rechallenge. As the assessor moves through the axes they accumulate points, individual scores from each of the axes are added together to give a total score, which in turn gives the probability of an ADR. The ADR is classified as definite, probable, possible or unlikely depending on the score. Individual judgement is still required to make decisions at each of the six stages of assessment. Levels of expertise and experience of the assessor may affect the results (Karch, Lasagna 1977).

The Naranjo tool (1981) (Table 1.1) is widely used for the assessment of causality. It consists of ten questions that are answered and a scoring system is applied to categorise ADRs as definite, probable, possible or doubtful. It classifies the likelihood that a reaction is related to a drug using concepts such as timing, evidence, history, dechallenge and rechallenge. Each question is weighted and the total score is used to categorise the reaction.

ADR cases are assigned a total score which determines the category as follows:

>9 = definite ADR

5-8 = probable ADR

1-4 = possible ADR

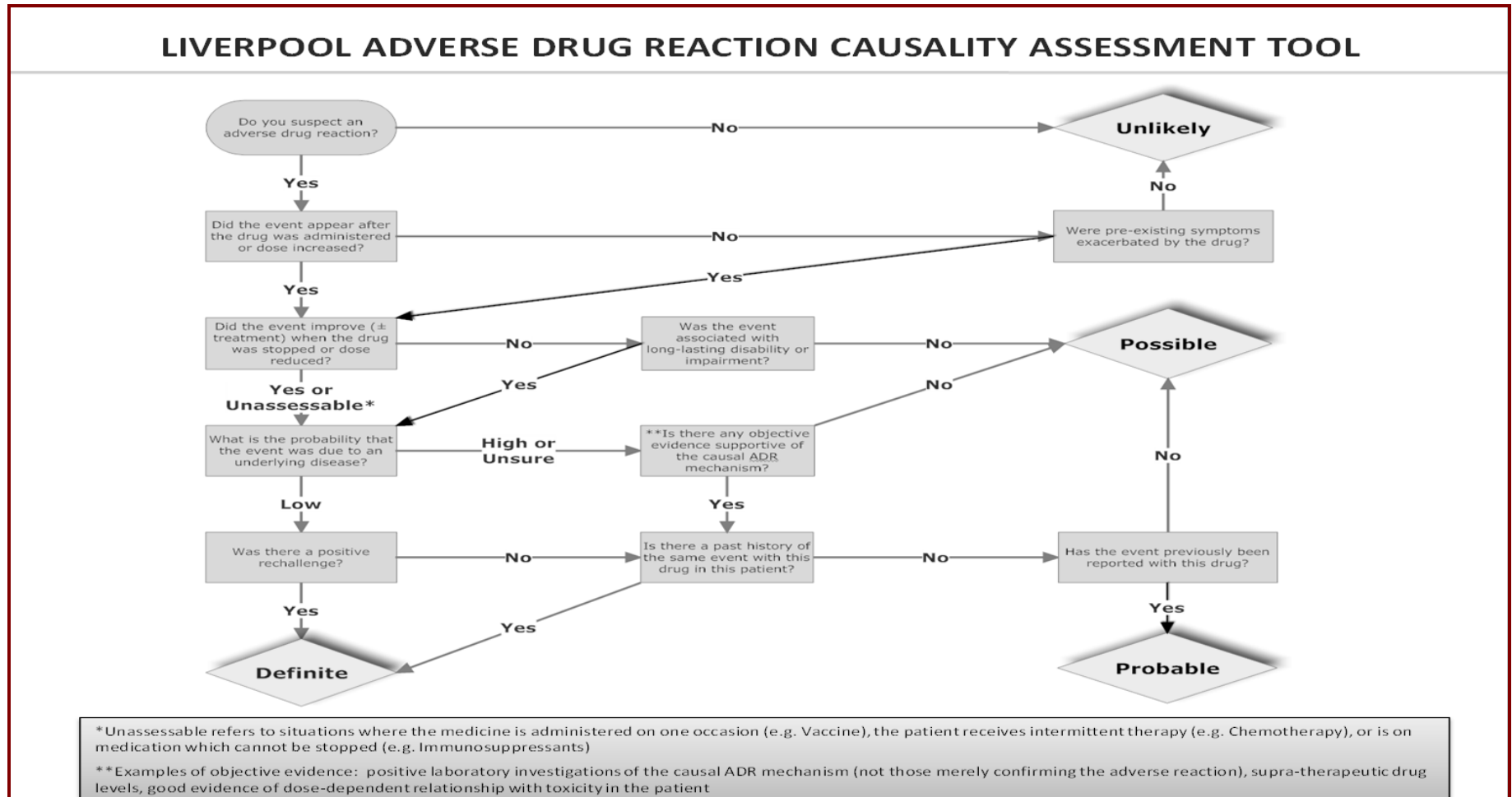
0 = doubtful ADR

Table 1.1 The Naranjo tool for ADR causality assessment (Naranjo et al. 1981)

Question number	Question	Yes	No	Don't know
1	Are there previous conclusive reports on this reaction?	+1	0	0
2	Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4	Did the adverse reaction reappear after the drug was readministered?	+2	-1	0
5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
6	Did the reaction reappear when a placebo was given?	-1	+1	0
7	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10	Was the adverse event confirmed by any objective evidence?	+1	0	0

During the ADRIC admissions study Gallagher et al. (2011) experienced some difficulties using the Naranjo tool. They found some questions were not appropriate which led to 'don't know' being selected which affected the scoring system used. As a result of this they set out to develop a new causality assessment tool that would overcome these problems and be easy to use. The team developed and validated a new tool the Liverpool Causality Assessment Tool (LCAT) (Gallagher et al. 2011a, Gallagher et al. 2011b). The LCAT tool (Figure 1.1) is a flow diagram which classifies ADRs as one of the four categories 'unlikely', 'possible', 'probable' or 'definite'. The LCAT was used to assess the causality in the two ADRIC observational studies (Gallagher et al. 2012, Thiesen et al. 2013)

Figure 1.1 The Liverpool adverse drug reaction causality assessment tool taken from (Gallagher et al. 2011a)



1.8.4 Bayesian methods

Bayesian approaches use specific findings in a case to transform a prior into a posterior probability of drug causation (Hutchinson 1991). A number of methods for diagnosis of ADRs use Bayes' theorem. The Bayesian Adverse Reaction Diagnostic Instrument (BARDI) which applies logic of uncertainty to causality assessment it was developed to overcome some of the limitations associated with the other methods. It is a decision analysis tool that calculates the posterior odds that a drug caused a particular event. The method has been found to be reproducible but the complex calculations are one of its limitations (Agbabiaka, Savovic & Ernst 2008).

1.8.5 Severity assessment

The severity of an ADR relates to the effect it has on the individual it is distinct from seriousness which is the extent to which the reaction causes harm. A severe reaction may not necessarily be serious. Severity assessments describe the clinical impact of ADRs. The terms 'mild', 'moderate' and 'severe' have been used to describe ADRs but these terms are rather subjective as they rely on the judgement of the assessor (Aronson, Ferner 2005). The Hartwig (1992) scale (Table 1.2) has been used in both the ADRIC observational studies to determine severity (Gallagher et al. 2012, Thiesen et al. 2013). The severity levels range from Level 1 (where the ADR required no change in treatment with the suspected drug); to Level 7 (the ADR was fatal). The scale is easy to use with clear definitions.

Table 1.2 Hartwig ADR severity assessment scale taken from (Hartwig, Siegel & Schneider 1992)

Level	Description
Level 1	An ADR occurred but required no change in treatment with the suspected drug.
Level 2	The ADR required the treatment with the suspected drug be held, discontinued or otherwise changed. No antidote or other treatment required. No increase in length of stay (LOS).
Level 3	The ADR required that treatment with the suspected drug be held, discontinued or otherwise changed, and/or an antidote or other treatment was required. No increase in LOS.
Level 4	a) Any level 3 ADR which increase LOS by at least 1 day. Or (b) The ADR was the reason for admission.
Level 5	Any level 4 ADR which requires intensive medical care.
Level 6	The adverse reaction caused permanent harm to the patient.
Level 7	The adverse reaction either directly or indirectly led to the death of the patient

Aronson and Ferner (2005) proposed a classification which asks specific questions about the ADR and the dosage regime of the suspected drug. It classifies severity by grade (1-3). It focuses on what needs to be done to manage the ADR by asking whether any change in the patient's treatment was required as a result of the ADR and whether the treatment was effective (Table 1.3).

Table 1.3 Proposed classification of ADR intensity (Aronson, Ferner 2005)

Grade	Change in dosage regimen of the offending drug	Treatability of the reaction
1	No change in dosage regimen required	A. No treatment required B. Relieved or partly relieved by treatment C. Not relieved by treatment
2	Altered dosage regimen required or desirable	A. No other treatment required B. Relieved or partly relieved by treatment C. Not relieved by treatment
3	Withdrawal required or desirable	A. No other treatment required B. Relieved or partly relieved by treatment C. Not relieved by treatment

Dormann et al. (2000) devised an ADR severity score. It classifies ADRs as mild, moderate or severe depending on the numerical score obtained when the algorithm is applied. It incorporates quality of life assessment. A score of 1 to 4 indicates a mild, a score of 5 to 8 a moderate, and a score of >8 a severe adverse drug reaction.

1.9 Avoidability assessment

1.9.1 Avoidability of adverse drug reactions – overview of the literature

Avoidability is an important concept in the study of ADRs (Ferner, Aronson 2010b). There is no universally accepted definition of avoidability or preventability as it is also called. The terms are often used interchangeably but for the purpose of this thesis the term avoidability has been used. There have been many attempts to devise tools or scales to help determine avoidability. As yet there is no 'gold standard'.

Definitions

Prevent: 'keep (something) from happening' (Oxford Dictionaries a) or to 'stop (something) from happening' (Merriam-Webster a).

Avoid: 'prevent from happening' (Oxford Dictionaries b) or to 'prevent the occurrence of' (Merriam-Webster b)

A systematic review carried out by Ferner and Aronson (2010) identified eight different approaches to defining avoidability in the literature:

1. analysis without explicit criteria
2. assessment by consensus
3. preventability linked to error
4. preventability linked to standards of care
5. preventability linked to medication-related factors
6. preventability linked to information technology
7. categorisation of harmful treatments in explicit lists
8. combinations of more than one of these approaches

These approaches rely on two general methods, judgement of one or more investigators or the use of pre-defined criteria. Both methods have limitations. In terms of consensus, it is possible for experts to agree but still be wrong. With avoidability related to standards of care, if the standards are poorly defined, it is difficult to determine avoidability (Ferner, Aronson 2010b).

They stated that nothing is absolutely avoidable but any intervention that reduces the probability of harm can be said to have made a contribution to prevention (Ferner, Aronson 2010). In a follow up paper, they outlined a novel method for determining avoidability (Aronson, Ferner 2010). This novel method involves classifying ADRs by mechanism and clinical manifestation to inform judgement about theoretical avoidability (Aronson, Ferner 2010). According to Ferner and Aronson complete analysis requires consideration of pharmacodynamic and pharmacokinetic mechanisms of the ADR, its time course, its dose-responsiveness and individual susceptibility factors (Ferner, Aronson 2010b, Aronson, Ferner 2010).

A systematic review conducted by Hakkarainen et al. (2012a) which looked at methods for assessing the avoidability of adverse drug events included 134 articles, 27% of these investigated avoidability of ADRs exclusively (excluding other ADE types). They found eighteen unique instruments for determining avoidability, which fell into four groups:

1. Instruments using a definition of avoidability only
2. Instruments with a definition of avoidability and an assessment scale for determining avoidability
3. Instruments with specific criteria for each avoidability category
4. Instruments with an algorithm for determining avoidability

Group 1: instruments using only a definition of avoidability, included three instruments (Dubois and Brook (1988), Bates et al. 1993 and Bates et al. 1995) which had no specific criteria for determining the type of preventability.

Group 2: instruments with a definition of avoidability and a scale for determining preventability category, five unique instruments were identified. In these instruments preventability of AEs was determined using a confidence scale or a Likert scale. Four out of the five were developed to assess preventability of AEs.

Group 3: included three instruments with specific criteria for each preventability category including Hallas et al. (1990). Two instruments had more than one category for preventable events. All three instruments in this group were developed for drug related AEs. Unlike any other instrument Hallas (1990) and colleagues included an unevaluable category for cases which data was not available or evidence was conflicting.

Group 4: instruments with an algorithm for determining preventability, seven instruments were found. All seven were developed for drug related AEs. Several of the instruments were modified from Schumock and Thornton (1992).

There is no standardised method for determining avoidability of an ADR, commonly used scales include Hallas (1990) (Figure 1.2) and Schumock and Thornton (1992) (Figure 1.3).

Figure 1.2 The Hallas Scale taken from (Hallas et al. 1990)

Hallas Scale

Definitely avoidable: The event was due to a drug treatment procedure inconsistent with present-day knowledge of good medical practice or was clearly unrealistic, taking the known circumstances into account

Possibly avoidable: The prescription was not erroneous but the event could have been avoided by an effort exceeding the obligatory demands

Not avoidable: The event could not have been avoided by any reasonable means, or was an unpredictable event in the course of a treatment fully in accordance with good medical practice

Unevaluable: The data for rating could not be obtained or the evidence was conflicting

Schumock and Thornton (1992) categorise avoidability based on a series of statements concerning possible contraindications, inappropriate dose, inappropriate monitoring, not considering previous history of a reaction to the drug, drug interactions, toxic drug levels and compliance. Answering yes to one or more of the statements categorises the ADR as preventable.

Figure 1.3 The Schumock and Thornton avoidability tool, taken from (Schumock, Thornton 1992)

Schumock and Thornton 1992

Yes to one or more indicates ADR may have been preventable

1. Was the drug involved in the ADR not considered appropriate for the patient's clinical condition?
2. Was the dose, route, and frequency of administration not appropriate for the patient's age, weight and disease state?
3. Was required therapeutic drug monitoring or other necessary laboratory testing *not* performed?
4. Was there a history of allergy or previous reactions to the drug?
5. Was a drug interaction involved in the reaction?
6. Was a toxic serum drug level documented?
7. Was poor compliance involved in the reaction?

Actions taken to standardise the assessment process were rarely described; 18/143 studies reported the use of an operational manual, guidelines or protocol for avoidability assessments. Physicians were reported to have conducted the assessments in 60% of the studies and pharmacists in 29% of studies, often a combination of both. 66% of articles had more than one assessor and an independent assessment was reported in 51% of studies. There is no consensus or guidance on the number of assessors required and whether assessments should be conducted by individuals or by groups. The hypothesis that group assessments are superior to individual assessment is tested in Chapter 3 of this thesis. Reliability of the assessments were reported in 27% of the articles overall and in three of the articles which looked at ADR avoidability (Hakkarainen et al. 2012a).

The ADRIC admissions study used the Hallas scale (1990) to assess avoidability (Gallagher et al. 2012). However, during the ADRIC inpatient study the need for developing a new avoidability assessment tool (AAT) was identified (Thiesen et al. 2013, Smyth et al. 2014). Difficulties were encountered answering certain questions as some of the questions cover consistency with 'good medical practice' which in paediatrics is difficult to answer due to the lack of guidelines available and deemed not appropriate; therefore this led to 'unevaluable' being selected regularly. Whilst the Hallas scale can be used in paediatrics as seen in the ADRIC admissions study it is sometimes difficult to apply for example the ADRIC inpatient study cases due to the complex language and types of ADR cases being assessed. The Hallas scale may be easier to use in the assessment of adult cases due to the number of guidelines available in the adult setting and therefore making the assessment of what constitutes "good medical practice" easier or less subjective than the assessment of paediatric cases.

A "good" avoidability assessment tool should be less subjective, easy to use and appropriate for use by less experienced reviewers. The criteria specified above are relevant to both adults and paediatrics. The LAAT although designed and tested for use in paediatrics is generalisable and applicable to other settings including adults. Our decision to develop a novel tool that was a flow diagram aimed to reduce or minimise the subjectivity involved in avoidability assessments. The difficulties encountered and the development of the LAAT is discussed in more detail in Chapter 2.

The systematic review by Smyth et al. (2012) highlighted the lack of studies performing an avoidability assessment. Out of 101 studies included in the review only nineteen assessed avoidability and there was wide variation in avoidability with 7-98% of ADRs being deemed as either possibly/definitely avoidable. Ten out of fourteen studies used a recognised avoidability tool with half using Schumock and Thornton (1992). Smyth et al. (2012) stated that further studies were required to determine which ADRs are potentially avoidable. However, they did not comment on specific requirements for assessing avoidability unlike Hakkarainen et

al. (2012a) who made recommendations for future studies which are discussed in more detail in Chapter 2. However, both studies commented on the importance of clear terminology and the importance of definitions to reduce heterogeneity and to allow comparisons between different studies.

A meta-analysis of the avoidability of ADRs in adults found that between 45-52% of ADRs were avoidable (Hakkarainen et al. 2012b). This study demonstrated that ADRs are a significant cause of morbidity and that effective intervention strategies are needed to prevent ADRs. The early detection of ADRs is important to avoid unnecessary harm to patients and knowledge of risk factors predisposing patients to ADRs is important to developing appropriate prevention strategies (Rashed et al. 2011).

1.9.2 Overview of paediatric studies that assessed avoidability

The ADRIC systematic review highlighted that few studies conducted an avoidability assessment (19/102). Data were only available for 14/19 studies as child only data were not available for four studies and ADR specific data was not provided by one study the studies are outlined in Table 1.4.

Table 1.4 Studies reporting avoidability data taken from systematic review by Smyth et al. (2012)

Causing admission studies						
Study	Country	Study duration/design	Clinical setting	Population	Causality	Avoidability assessment
Easton 2004 ¹	Australia	22 weeks Prospective	Specialist paediatric teaching hospital and general regional teaching hospital	Children Not reported – 17 years	Dartnell et al. 1996	Schumock and Thornton 1992 127 DRPs, 29/127 were ADRs 10.3% ADRs preventable 46.9% DRP preventable
Gallagher 2011	UK	2 weeks Prospective	Large tertiary - paediatric hospital	Children <18 years	Naranjo	Hallas et al. 1990 33% Possibly avoidable 67% Unavoidable
Gallagher 2011 ²	UK	12 month Prospective	Large tertiary - paediatric hospital	Children <18 years	Liverpool ADR Causality Assessment Tool (LCAT)	Hallas et al. 1990 22.1%
Al-Olah 2008	Saudi Arabia	28 days Prospective	Causing admission Emergency department	Children and adults Not reported in publication/unable to obtain from author	Naranjo	Definite preventable and definite non-preventable defined as 3 evaluators in agreement; possible preventable and possible non-preventable 2 in agreement

¹ Easton (2004) cited in Table 4 of systematic review by Smyth et al. (2012) as Easton-Carter but referenced as Easton (2004) in their reference list

² Gallagher (2012) cited in Table 4 of systematic review by Smyth et al. (2012) as Gallagher (2011) as unpublished at time of publication of the systematic review

Table 1.4 Studies reporting avoidability data taken from systematic review by Smyth et al. (2012) (continued)

In hospital studies						
Choonara 1984	UK	6 months Prospective	General paediatric ward	Children Not reported in publication/unable to obtain from author	Seidl et al. 1966	6/15 ADRs were avoidable (40%) 3 dose prescribed was too high, 1 treatment not necessary, 2 application of pharmacological principles would have prevented reactions
Easton-Carter 2003b	Australia	39 weeks Prospective & prospective	General paediatric ward	Children 0–17 years	Naranjo Score	Schumock and Thornton 1992 9.8% avoidable
Gonzalez-Martin 1998	Chile	1 year Prospective	Paediatric wards	Children 5 days–15 years	Naranjo Score	Naranjo and Busto 1989 93% dose dependent
Neubert 2004	Germany	8 months Prospective	Paediatric isolation ward	Children 5 days–17 years	Naranjo Score	Adapted version Schumock and Thornton 1992 Preventable 21.7% Not preventable 50% Tolerated 28.3%
Community Studies						
Easton-Carter 2003a	Australia	18 weeks Prospective	Emergency department	Children < 17 years	Dartnell et al. 1996	Schumock and Thornton 1992 280 DRPs 118/280 were ADRs 51.3% preventable for all DRPs 36.9% not preventable for all DRPs 30.5% for ADRs

Table 1.4 Studies reporting avoidability data taken from systematic review by Smyth et al. (2012) (continued)

Kramer 1985	Canada	1 year Prospective	Private group practice	Children 2 days–18.9 years	Kramer 1979	Highly preventable - realistic nondrug alternative available; Probably preventable - safer alternative drug available/lower dosage; Possibly preventable - Dose might have been modified; Unpreventable - would not have changed the choice/dose of drug. 77% highly/probably/possibly avoidable
Planchamp 2009	France	6 months Prospective	Emergency department	Children 0–18 years	Begaud et al. 1985	Olivier et al 2005 7%
Combined settings (causing admission and in hospital)						
Baniasadi 2008	Iran	12 month prospective	Multidisciplinary hospital	Children and adults 0–18 years	Naranjo Score	Schumock and Thornton 1992 22.3% both adults and children
Oshikoya 2007	Nigeria	3 years both	General paediatric ward	Children 4 months–12 years	Jones 1982	Done but no reference provided 44 ADRs detected and 43/44 deemed preventable (98%)
Van der Hooft 2008	Netherlands	1 year Retrospective		Children and adults Not reported -16 years	WHO	Hallas et al. 1990 115 ADRs total, 1 detected <16s 30% over 17s- adults 0% ADRs avoidable <16s

1.9.2.1 Studies of ADRs causing admission

A prospective study of drug related problems (DRPs) causing admission over 22 weeks to two hospitals (a specialist paediatric teaching hospital and a general regional teaching hospital) in Australia (Easton KL, Chapman & Brien 2004). DRPs were classified according to the eight categories defined by Strand et al. (1990) which include 'resulting from an adverse drug reaction' (category 5). DRPs were assessed by a multidisciplinary panel. The panel consisted of seven independent members from a variety of disciplines including paediatric medicine, pharmacy, paediatric clinical pharmacology and nursing. Two members of the panel reviewed each case on an independent basis. At least one was required to be a medical practitioner. In cases where discrepancies arose, the reviewed cases were discussed by panel members to reach a consensus. The consensus opinions were recorded as the final DRP category, causality and preventability classifications. Schumock and Thornton (1992) algorithm was used to assess avoidability. One hundred and twenty seven cases were deemed to be caused by a DRP of these, twenty nine were categorised as ADRs. Three out of the twenty nine ADRs (10.3%) were assessed as avoidable.

A pilot study which looked at ADRs causing admission conducted by Gallagher et al. (2011a) was conducted over a two week period. The Edwards and Aronson (2000) definition of an ADR was used. All unplanned admissions to the main hospital and to the accident and emergency observation ward were included. The study team collected information for each patient including any medication taken in the preceding two weeks. Over the two week period there were 822 acute admissions to the hospital, 473 to the main hospital wards and 349 to the observation ward subsequently discharged home. There were 27 admissions identified as being complicated by an ADR which occurred in 25 patients. There were 19 admissions to the main hospital and 8 to the observation ward. The estimated incidence of admissions to the main hospital wards related to an ADR was 4% and 2.3% for the observation ward. The ADRs were assessed for causality, severity and avoidability. The Hallas scale (1990) was used to determine avoidability 33% of the ADRs were

classified as 'possibly avoidable' and 67% were deemed unavoidable. No ADRs were found to be 'definitely avoidable'. The study team reported that Hallas classification was easy to use but due to its broad classification terms it was likely to be user-dependent (Gallagher et al. 2011a).

Gallagher et al. (2012) conducted a prospective study in a large tertiary children's hospital over a one year period. All unplanned admissions were prospectively screened for ADRs. Patients admitted to the accident and emergency department short-stay observation ward were not included. The Edwards and Aronson (2000) definition of an ADR was used. The incidence of ADRs causing admission was 2.9%. They detected 249 ADRs and assessed them for causality, severity and avoidability. The Hallas scale (1990) was used for assessing avoidability; this was done via a consensus group. 22.1% of the ADRs were classified as possibly or definitely avoidable.

Al-Olah and Al Thiab (2008) undertook a 28 day prospective, observational study which looked at DRPs causing admission to the emergency department. The study included adults and children. The study team was made up of two clinical pharmacists and one physician. They defined a DRP as *'an event or circumstance involving drug treatment that actually or potentially interfered with the patient experiencing an optimum outcome of medical care'*. They included ADRs in DRP and they defined an ADR as *'a medical problem resulting from an adverse effect(s)'* (Al-Olah, Al Thiab 2008). A definite DRP was defined as three reviewers in agreement, a possible DRP was defined as two reviewers in agreement following a consensus meeting. The same applied to avoidability of DRPs, definite preventable and definite non-preventable were defined as three reviewers in agreement and possible preventable and possible non- preventable DRPs were defined as only two reviewers in agreement. A total of 557 patients were admitted during the study period, 82 (14.7%) were due to a DRP. The adult to paediatric ratio was 50:32. ADRs were the second most common DRP accounting for 24.5%. Six ADRs occurred in children, 17% were deemed possibly preventable and 83% were deemed definitely

no-preventable. The reason provided for the possibly preventable ADR was the drug not being prescribed as per treatment protocol.

1.9.2.2 Studies of ADRS among in-patients

Choonara and Harris (1984) conducted a 6 month study investigating ADRs in medical inpatients in a paediatric hospital (Choonara, Harris 1984). Medical and nursing staff prospectively looked for ADRs on the daily ward round. An ADR was defined according to the criteria used by Seidl et al. (1966). Over the six month period 268 children were admitted and 15 suffered a probable or definite ADR. Six of the fifteen ADRs were deemed avoidable, in three cases the dosage prescribed was too high and in two cases application of pharmacological principles could have prevented the ADRs and in the final case the treatment was deemed not necessary.

A study investigating the frequency of ADRs in the inpatient population of three Australian hospitals (Easton-Carter, Chapman & Brien 2003a) considered all paediatric patients admitted to wards of three hospitals for inclusion, excluding oncology patients. ADRs were identified using two methods: spontaneous monitoring and retrospective intensive monitoring. An independent panel reviewed information collected on reactions and established the causality, clinical significance and preventability of ADRs arising amongst inpatients. Of the 17,432 eligible patients, 41 (0.2%, 95 % CI 0.1-0.3%) were determined by an independent panel to have experienced ADRs. Avoidability was assessed using the Schumock and Thornton (1992) criteria and 9.8% of the ADRs were considered preventable.

A prospective study which aimed to determine the frequency and characteristics of ADRs in hospitalised children conducted in Chile between January and December 1997. The study included children aged 0 to 16 years receiving drug treatment. Data were collected by a clinical research pharmacist on a daily basis. Medication histories including past and present medicines were gathered by the pharmacist by interviewing the parent or guardians on admission. ADRs were defined according to the WHO definition. Suspected ADRs were evaluated by the pharmacist and then

discussed with a clinical pharmacologist. 13.7% of 219 patients experienced one or more ADR(s) during their hospital stay. In total 46 ADRs were detected; 13.6% were definite, 54.2% probable and 32.2% were possible. The mechanisms of ADRs were classified as dose-dependent: *'the frequency and severity of the ADRs are directly proportional to the administered dose and therefore can be prevented and/or treated by adjusting the dose, and not dose related: a reaction due to an increased susceptibility of the patient'* (Naranjo CA 1989). 93% of ADRs in the study were classified as dose dependent. Twenty four drugs were involved in the ADRs, 38/46 ADRs were due to a single drug and the remaining eight involved two drugs. No further details were reported on the assessments.

Neubert et al. (2004) conducted a prospective study in Germany over eight months in 2001. The setting was a ten-bed paediatric ward, patients <18 years were included and the WHO (1972) definition of an ADR was used. ADRs were identified by a weekly review of patient charts; this was conducted by a team comprised of a clinical pharmacologist, a pharmacist and a paediatrician. Forty-six ADRs were detected in 31 patients, representing an ADR incidence of 17.4%. Suspected ADRs were assessed using an adapted version of the Schumock and Thornton (1992) avoidability criteria. All preventable ADRs with a benefit greater than risk were classified as tolerated. Overall 21.7% were classed as preventable, 50% were not preventable and 28.3% were categorised as tolerated (Neubert et al. 2004).

1.9.2.3 Community studies

A prospective multicentre study carried out over 18 weeks in Australia (Easton-Carter, Chapman & Brien 2003b). The study included children aged seventeen and under attending the emergency department of one of the three sites (a specialist paediatric teaching hospital, a general suburban teaching hospital and a general regional teaching hospital). They considered DRPs according to the eight categories defined by Strand et al. (1990). An emergency department attendance was considered a study case if the association between the attendance and a DRP was established. Over the data collection period 280 cases were assessed by the

multidisciplinary panel to have had a DRP. Of these 118 were categorised as ADRs. Causality and avoidability assessments were carried out by the panel. They used Schumock and Thornton (1992) to assess avoidability 36/118 ADRs were considered avoidable. Interestingly antibiotics were involved in 34 of the 36 ADRs.

Kramer et al. (1985) carried out a prospective study over a one year period which employed active patient follow up to monitor for adverse drug reactions in a community setting. Patients visiting the practice were invited to take part in the study. Courses of therapy were classified as either short term ≤ 1 month or long term > 1 month. For short term courses, follow up monitoring was conducted at 2 weeks or at the anticipated end of therapy and at completion of treatment. For long term courses monitoring calls were made at 2 weeks and 1, 3 and 5 months after starting treatment. No definition of an ADR was provided. The ADR incidence was 11.1% in the study population. Two hundred ADRs were categorised as probable or definite. Avoidability assessments were carried out for all definite or probable ADRs by the senior author and prescribing physician. ADRs were classified as follows: Highly preventable - realistic nondrug alternative available; Probably preventable - safer alternative drug available/lower dosage; Possibly preventable - dose might have been modified; Unpreventable - would not have changed the choice/dose of drug (Smyth et al. 2012). Out of the 200 ADRs assessed by the senior author, 12 were deemed highly preventable, 83 were probably preventable, 59 possibly preventable and 46 were deemed unpreventable and overall 77% were deemed preventable. The distribution of responses was similar when the prescribing physician conducted the assessments, although agreement on a case by case basis was reported as fair (Kramer, Hutchinson & Flegel 1985).

Planchamp et al. (2009) conducted a six month prospective study of children attending the emergency department. The regional pharmacovigilance centre and the department of clinical pharmacology prospectively recorded all potential ADRs among patients under 18 years old in the paediatric emergency unit reported at the daily staff meetings. All cases were then screened and validated by the regional pharmacovigilance centre. Confirmed ADR cases were assessed for avoidability,

seriousness, and off-label use. Ninety children presented with potential adverse drug events and ADRs were confirmed in 43 patients. Avoidability was assessed using the algorithm from Olivier et al. (2005). Three ADRs (7%) were deemed avoidable (Planchamp et al. 2009).

1.9.2.4 Combined Settings (causing admission and in hospital)

Baniasadi et al. (2008) conducted a study in a 250 bed, tertiary care, multidisciplinary teaching hospital. The study included both children and adults. The aim was to establish an ADR reporting and monitoring centre. The study encouraged the reporting of ADRs over a 12 month period through ADR reporting yellow forms, via a rapid telephonic reporting system or direct reporting to the pharmacovigilance team. An ADR was defined according to the WHO (1972) definition. Each ADR was assessed for causality, severity and avoidability. The avoidability assessments were conducted using the criteria defined by Schumock and Thornton (1992). Over the study period a total of 6840 patients were admitted and 112 ADRs were reported. Thirty six patients aged 0-18 experienced an ADR. Overall 22.3% of the ADRs were classified as avoidable, the percentage breakdown of avoidable ADRs in children was not available (Baniasadi, Fahimi & Shalviri 2008).

A study by Oshikoya et al. (2007) used data pooled from two studies; a retrospective medical record review of paediatric admissions and a prospective observational study of admissions. The prospective study included a six month data collection period which looked at all patients admitted to the paediatric ward with a stay greater than 24 hours. The retrospective study was performed using the hospital admissions records which looked at a two year period from 2004 to 2006 and identified children with an ADR whether it was present on admission or occurred during a hospital stay. ADRs were defined according to the WHO (1972) definition. Causality assessments were carried out using the criteria by Jones (Jones 1982). The incidence of ADRs causing admission was 0.45% and 0.71% for ADRs in hospital. In total 44 children were reported to have experienced an ADR. Twenty eight ADRs were deemed definite, twelve probable and four possible. 98% of the

ADRs were categorised as avoidable however, no information was provided on the assessments and how they were conducted or what criteria were used. The most commonly reported ADRs during the study period were skin related with erythema multiforme and a pustular rash accounting for almost 55% of cases (Oshikoya KA et al. 2007).

A study by van der Hooft et al. (2008) looked at ADR related admissions over a one year study period in 2003. The study was retrospective and included patients (adults and children) from an Integrated Primary Care Information (IPCI) database, a General Practitioner (GPs) research database which included data from electronic patient records of approximately 150 GP surgeries. Patient records and hospital discharge summaries were reviewed for ADRs. The research team was comprised of research assistants and four doctors. The team evaluated discharge letters each letter was reviewed independently by two doctors; where discharge letters were not available electronic patient records were used to gather the required information. Consensus meetings were held and where any disagreement occurred either in causality or avoidability assessments discharge letters were re-evaluated if agreement could not be reached then a third doctor was consulted and their decision was taken as definitive. Causality assessments were completed using the WHO criteria (World Health Organisation 1969) and avoidability assessments were conducted using Hallas et al. (1990). In total 3609 hospital admissions occurred in the study population during the study period however, 94 cases were excluded due to lack of information. Of the remaining 3515 admissions, 122 ADRs were detected and 115 were acute. One ADR occurred in children under 16 years of age, it was deemed not avoidable. 24 ADRs occurred in the 17-55 age group but the breakdown of how many occurred in patients under 18 was not available. 35/115 ADRs were categorised as avoidable (van der Hooft et al. 2008).

1.9.2.5 Other paediatric studies which have assessed ADR avoidability identified from a systematic review of inpatient ADRs in adults and children by Khan (2013)

The systematic review by Khan (2013) included 51 studies from 2000 to April 2013. The review aimed to investigate the comparative impact of hospital acquired ADRs in adults and children in terms of economic implications and to describe incidence, severity, morbidity, mortality and preventability of the ADRs. ADRs were defined using the WHO (1972) definition. In their description of studies which conducted avoidability assessments they cited the systematic review by Smyth et al. (2012) and stated that various individual studies of ADRs in hospitalised children have shown different avoidability rates. Two additional studies were mentioned Temple et al. (2004) and Priyadasini et al. (2011). The study by Banisaddi et al. which was included in the review by Smyth et al. (2012) was also mentioned although child specific data relating to avoidability was not available. It was not clear from the paper if they had included other studies which looked at avoidability but no others were mentioned (Khan 2013).

Other studies

A study conducted in the US by Temple et al. (2004) which looked at the frequency and avoidability of ADRs over a six year period from 1994 to 1999 found the incidence to be 0.85 ADRs per 100 admissions. 20.7% of the ADRs reported were avoidable. Avoidability was assessed using the Schumock and Thornton (1992) criteria and two assessors reviewed the cases for avoidability.

An observational study conducted in the paediatric department of a tertiary hospital which included all children under 12 inpatients and outpatients. Inpatients included those who were admitted as a result of an ADR and those who experienced an ADR during their hospital stay. Over the study period July to September 2009, 30 ADRs were recorded. Causality, severity and avoidability were assessed for the ADRs. A modified version of the Schumock and Thornton (1992) criteria was used to assess preventability. The majority of ADRs were categorised as probable preventability (87%) and 3% were definitely preventable. Overall 90% of ADRs were deemed preventable (Priyadharsini et al. 2011).

1.9.2.6 Results from the Hakkarainen et al. (2012a) systematic review

Hakkarainen et al. (2012a) conducted a systematic review of methods for assessing the avoidability of ADEs (described earlier in section 1.7.7). The review included 38 studies which investigated the avoidability of ADRs. Of these eight studies used Hallas et al. (1990), three used Imbs et al. (1998) and fifteen used Schumock and Thornton (1992). Both adult and paediatric studies were included; details of the individual studies are outlined in table 1.5.

Table 1.5 Summary of studies included in the systematic review by Hakkarainen et al. (2012a) which assessed avoidability of ADRs in adults or children

Authors	Country	Study design	Population	Avoidability
Calderon-Ospina et al. 2010	Colombia	Cross-sectional Observational	≥ 18 years	Schumock and Thornton (1992) 50%
Farcas et al. 2010	Romania	Prospective observational	25-92 years	Imbs et al. (1998) 50%
Jonsson et al. 2010	Sweden	Retrospective observational	26-85 years	Hallas et al. (1990) 26%
Lopez et al. 2010	Colombia	Prospective observational	≥ 18 years	Dormann et al. (2003)
Davies et al. 2009	United Kingdom	Prospective observational		Hallas et al. (1990) 53.3%
Pourseyed et al. 2009	Iran	Prospective observational	13-91 years	Schumock and Thornton (1992) 50%
Alexopoulou et al. 2008	Greece	Prospective observational	15-100 years	Chan et al. (2001) 42.9%
Al-Malaq et al. 2008	Saudi-Arabia	Retrospective observational	1 month- 80 years 24.7% of cases were in children <18 years	Preventability by Type A, B, C 60% (adults + children) Paediatric specific data not available
Baniasadi et al. 2008	Iran	Prospective, observational	Adults and children	Schumock and Thornton (1992) 22.3% (adults + children) Paediatric specific data not available
Franceschi et al. 2008	Italy	Prospective observational	≥65 years	Hallas et al. (1990) and integrated by Gurwitz et al. (2000) 76.5%
Hopf et al. 2008	United Kingdom	Prospective observational	19-91 years	Hallas et al. (1990) 83.3%
Joshua et al. 2008	India	Prospective observational	Adults	Schumock and Thornton (1992) 19.6%
Mehta et al. 2008	South Africa	Prospective observational	>16 years	Schumock and Thornton (1992) 53% causing admission 33.3% hospital inpatients
Ruiz et al. 2008	Spain	Prospective observational	Children were excluded	Schumock and Thornton (1992) 34.6%
Subish et al. 2008	Nepal	Retrospective observational	Adults and children	Modified Schumock and Thornton (1992) and Lau et al. (2003) 9.09% (adults + children) Paediatric specific data not available
Van der Hooft et al. 2008	Netherlands	Retrospective observational	Adults and children	Hallas et al. (1990) 30% for adults 0% for children
Grenouillet-Delacre et al. 2007	France	Prospective observational	>15 years	48% (adults + children) Paediatric specific data not available
Patel et al. 207	India	Prospective observational	>18 years	Hallas et al. (1990) 59.62%

Table 1.5 Summary of studies included in the systematic review by Hakkarainen et al. (2012) which assessed avoidability of ADRs in adults or children (continued)

Rivkin 2007	United States	Prospective observational	Not reported	Schumock and Thornton (1992) 86%
Davies et al. 2006	United Kingdom	Prospective observational	Adults	Hallas et al. (1990) 59%
Hanlon et al. 2006	United States	Prospective intervention	Male >65 years	37.63%
Jose et al. 2006	India	Retrospective observational	Children and Adults	Lau et al. (2003) 28.7% (adults + children) Paediatric specific data not available
Dormann et al. 2004	Germany	Prospective observational	18-97 years	Schumock and Thornton (1992) 44.3%
Pirmohamed et al. 2004	United Kingdom	Prospective observational	>16 years	Hallas et al. (1990) 72%
Temple et al. 2004	United States	Retrospective observational	Paediatric	Schumock and Thornton (1992) 20.7%
Dormann et al. 2003	Germany	Prospective observational	17-97 years	Schumock and Thornton (1992) 41.2% >65s 65.7% <65s
Easton-Carter et al. 2003b	Australia	Retrospective observational	Paediatric	Schumock and Thornton 1992 9.8%
Easton-Carter et al. 2003a	Australia	Prospective observational	0-17 years	Schumock and Thornton 1992 30.5%
McDonnell et al. 2002	United States	Retrospective observational	Children and adults ≤15	Adapted from Schumock and Thornton (1992) 62.3% (adults and children) Paediatric specific data available not available
Olivier et al. 2002	France	Prospective observational	>15 years	Imbs et al. (1998) 34% Paediatric specific data available not available
Letrilliart et al. 2001	France	Prospective observational	0-99 years	Imbs et al. (1998) 59% Adults 0% for the 1 ADR detected in a child aged 15
Wasserfallen et al. 2001	Switzerland	Prospective observational	16-93 years	Livio et al. (1998) 32%
Lagnaoui et al. 2000	France	Prospective observational	15-94 years	Dubois and Brook (1988) 81.2%
Gholami et al. 1999	Iran	Prospective observational	excludes children <10	Criteria adapted from Schumock and Thornton (1992) 58.8% 5.9 % in ages 10-25 years
Schumock et al. 1995	United States	Prospective observational	Not reported	Mean rate 21.25%
Pearson et al. 1994	United States	Prospective observational	Adults	19%
Kramer et al. 1985	Canada	Prospective observational	0-18 years	Highly preventable Probably preventable - Unpreventable 77%
Choonara et al. 1984	United Kingdom	Prospective observational	Paediatric	Judgement 40%

1.9.2.7 Other studies which assessed avoidability

The ADVISE study (previously described in Section 1.61) conducted avoidability assessments using the Schumock and Thornton (1992) criteria. All assessments of ADRs were carried out by the local research team in each country. Overall 16.6% of ADRs identified were categorised as avoidable. Avoidability rates ranged from 4.3% to 33.3% in the different countries; Australia reported the highest rate of avoidable ADRs and Malaysia reported the lowest rate of 4.3% (Rashed et al. 2012).

An 8 month prospective study was conducted at a ten bed paediatric isolation ward of a University hospital (Weiss et al. 2002). Charts were reviewed once weekly by the study team. ADRs were defined according to the WHO (1972) definition. A total of 68 ADRs were detected in 46 of 214 patients. An adapted version of the Naranjo algorithm was used to assess causality. ADRs were classified as predictable or unpredictable, predictable ADRs may either be avoidable or tolerated, implying such events as toxicity, drug interactions, and secondary effects. Unpredictable and usually unavoidable ADRs include idiosyncratic or allergic reactions as well as intolerance. 24% of the ADRs were judged to be avoidable, 29% to be unavoidable, and the majority, 47% events to be tolerable.

1.9.3 Incidence of avoidable ADRs in Adults

A meta-analysis conducted in 2010 on preventable ADRs in adults showed that approximately half of ADRs among adult inpatients and outpatients may be avoidable (Hakkarainen et al. 2012b). The study also highlighted the lack of evidence on avoidable ADRs. The study confirmed that ADRs are a significant burden to healthcare among adults. No similar study has been done in paediatrics but studies suggest similar incidence rates.

1.10 Conclusion

In summary, adverse drug reactions are a significant problem in children. The available instruments for the assessment of avoidability of ADRs vary in reliability and validity (Smyth et al. 2012). The assessment of avoidability is compromised by a lack of consensus on the definition of avoidability and associated heterogeneity in underpinning methodology for instrument development (Hakkarainen et al. 2012a). No instruments are available specifically for characterisation of ADRs in children and young people, and there is a requirement to develop such instruments. There is a lack of data on avoidability of ADRs in children and there is wide variation between studies where data were available (Smyth et al. 2012). Given the burden of ADRs in children further work is needed to address how ADRs in children may be prevented in the future. Our experience with the Hallas approach indicated the need to develop a new method to assess avoidability in children.

1.11 Aim and objectives of thesis

1.11.1 Aim

The aim of this thesis was to describe the avoidability of ADRs in children and methods used to assess avoidability.

1.11.2 Objectives

- 1 To develop and test a new avoidability assessment tool that is more suitable for use in paediatrics but which is also generalisable and applicable to a variety of other settings.
- 2 To conduct reliability and validity testing on the new tool as per recommendations by Hakkarainen et al. (2012a)
- 3 To test the hypothesis that group assessments are superior to individual avoidability assessments.

- 4 To assess the avoidability of the ADRIC admissions study cases using the newly developed Liverpool avoidability assessment tool and to compare the results to the existing Hallas assessments carried out as part of the ADRIC programme.
- 5 To identify potential strategies for clinical practice that might reduce the incidence of ADRs.

Chapter 2: Development of the Liverpool Adverse Drug Reaction Avoidability Assessment Tool (LAAT)

2.1 Introduction

The prevention of avoidable harm due to ADRs is a prime clinical motivation for studying drug safety. According to the World Health Organisation (WHO), ADRs rank among the top ten leading causes of mortality in some countries (World Health Organisation 2004b). Patient and medication safety is high on the agenda of the European Medicines Agency (EMA) (European Medicines Agency 2011a), the Council of Europe (Expert Group on Safe Medication Practices 2006) and the WHO (World Health Organisation 2004b). The WHO has identified some key areas including measuring harm, understanding causes, identifying solutions, evaluating impact and translating evidence into safer care (World Health Organisation 2004b). A meta-analysis of avoidable ADR studies conducted by Hakkarainen et al. (2012b) concluded that avoidable ADRs are a significant burden to the healthcare system and a cause of morbidity among outpatients. They found that roughly half of all ADRs amongst adult inpatients (45%) and outpatients (52%) may be avoidable (Hakkarainen et al. 2012b).

The importance of examining avoidability of ADRs became clear from two sources. Firstly, the ADRIC systematic review indicated that few previous studies (19/101) had examined avoidability and those that had, used inconsistent methods (Smyth et al. 2012). The review concluded that the available instruments for assessment of avoidability of ADRs vary in reliability and validity (Smyth et al. 2012). Secondly, difficulties were encountered during the assessment of avoidability using existing tools in the ADRIC inpatient study (Thiesen et al. 2013). The study of avoidability is complex. A key factor for this complexity is that there is no universally accepted definition for avoidability (Ferner, Aronson 2010b). Ferner and Aronson (2010) stated there are two aspects to avoidability: whether or not in principle an event is avoidable, in the absence of error and, if it is, whether or not we can, in fact, prevent it. They gave the example of penicillin hypersensitivity reactions, which, in

principle, can be avoided in patients who are known to be susceptible, by not giving the drug; however, in practice these reactions can still occur owing to lack of information available to the prescriber (Ferner, Aronson 2010b). Ferner and Aronson (2010) concluded in their systematic review that several definitions exist and none fits all circumstances.

There have been many attempts to devise tools or scales to help determine avoidability including those by Hallas (1990), Schumock and Thornton (1992), Dormann et al. (2003), Ducharme et al. (2007) and Olivier et al. (2005). Commonly used scales include: Hallas (1990) and Schumock and Thornton (1992) which are based on appropriateness of prescribing or treatment choice.

Hakkarainen et al (2012a) reported while there was wide variation in the methods used they all shared a common theme; the basis for defining avoidability whether an error or sub-standard care had resulted in an ADE (Hakkarainen et al. 2012a). Despite the importance of avoiding ADRs, this area remains under-researched. This may be attributable to the methodological problems in the area, which Hakkarainen et al (2012a) have summarised in a systematic review on methods for assessing the avoidability of ADEs. They listed inconsistent terminology as one of the problems; there is wide variation in the terms and definitions used (ADRs, ADEs etc.) and this hinders the interpretation and comparison of studies. In their review they used the term ADE which included ADRs and other AEs related to medications (Hakkarainen et al. 2012a).

In the ADRIC admissions study Gallagher et al. (2012) used the Hallas scale (1990) (Figure 1.2) to determine avoidability and found that 78% of ADRs were unavoidable, and 22% were either possibly or definitely avoidable. They suggested some potential prevention strategies for ADRs based on their assessment of the ADRs they classed as 'definitely avoidable'- that more careful attention to practical aspects of care, such as improved monitoring, following prescribing guidelines and improved patient education, could lead to a reduction in the frequency of ADRs causing admission (Gallagher et al. 2012). The Hallas scale was chosen for the ADRIC

admissions study as it has been used previously in ADR studies by other investigators (Smyth R et al. 2014). Assessment of avoidability was undertaken by consensus approach using the definitions by Hallas et al. (1990) (Gallagher et al. 2012). The Hallas criteria are less prescriptive than some other avoidability tools. The definitions, which are based on avoidability linked to standards of care, are wide and may lead to variability in assessor rating.

The need for developing a new avoidability assessment tool (AAT) was identified during the ADRIC inpatient study when we tried to use the Hallas scale (1990) to determine avoidability (Thiesen et al. 2013). The Hallas scale (1990) is a series of four statements linked to standards of care (Figure 1.2). In particular we encountered difficulties with some of the language and mechanisms for judging avoidability. For example, the ADRIC team (comprised of a paediatrician, a paediatric research nurse and at least one paediatric research pharmacist) suggested that in some cases it was difficult to agree about the nature of 'present day knowledge of good medical practice'. Specifically, Hallas was difficult to use in the inpatient study as treatment was often guided by tertiary paediatric specialist advice. 'Present day knowledge of good medical practice' of treatments for paediatric diseases covers a vast range of information. Comprehensive awareness of the information required to assess avoidability of ADRs would require extensive reading and synthesis of information. Many paediatric conditions are rare or ultra-rare which makes information difficult to locate. In contrast, the ADRIC admissions study predominantly involved a relatively small number of common acute conditions that the research team were familiar with, or, a relatively small number of acute complications of chronic illnesses that the research team were familiar with.

Also, due to the much smaller number of ADR cases (249) detected in the admissions study it was possible to hold consensus meetings to discuss the avoidability of each ADR case report and using the Hallas (1990) tool assign an avoidability outcome. The consensus meetings involved senior members of the

ADRIC investigating group. It would not have been feasible in the inpatient study to hold consensus meetings due to the much larger number of ADR cases (1446).

On other occasions, the study team found it difficult to agree on whether an event could have been avoided by 'an effort exceeding obligatory demands'. This was partly because of different perceptions of the 'obligatory demands' in particular clinical settings and partly because there were a range of opinions about whether extra effort would have made a difference to the occurrence of an ADR. In the ADRIC admissions study, 17.7% of ADRs were associated with prescriptions originating from community, 34.1% originating from hospital for non-oncology related conditions and 48.2% were prescriptions originating from oncology (Gallagher et al. 2012). The most common ADRs in the ADRIC admissions study were oncology related and there was clarity about nature of standard practice. In the ADRIC inpatient study opioid analgesics and drugs used in general anaesthesia (GA) accounted for more than 50% of all drugs implicated in ADRs (Thiesen et al. 2013). Analgesia and anaesthesia are usually tailored to the needs of the child and the clinical context. The nature of obligatory demands and the effort required to meet or exceed obligatory demands depend on the circumstances of the individual case. The information about each ADR case was not sufficient to allow judgments about obligatory demands. It may not be feasible to gather this information in research or clinical settings.

For example, a variety of anaesthetic-related factors have been implicated in producing increased post-operative vomiting (POV) in children. However, few of these factors are included in any of the POV risk scoring systems for paediatric patients. The use of inhaled anaesthetic agents has been linked with an increased risk of emesis particularly in children who have other risk factors for POV. It is recommended that total intravenous anaesthesia is considered for children who are at high risk of POV undergo surgery that has a high risk of producing POV (The Association of Paediatric Anaesthetists of Great Britain & Ireland 2009). Also the use of opioid analgesia in theatre may be associated with an increased risk

of POV and the Association of Paediatric Anaesthetists (APA) recommend that anaesthetists try to minimise the use of opioid analgesia where possible in high risk patients. Using the Hallas score to assess avoidability of POV cases proved difficult in the ADRIC inpatient study, as it was difficult to assess the nature of obligatory demands given the individual nature of these cases.

Another factor was the issue of guidelines. Paediatric guidelines do not exist for many therapeutic areas included in the ADRIC inpatient study. If a guideline could be identified, it rarely contained information about prevention of ADRs. This situation was different from the ADRIC admissions study in which almost half of the ADRs were oncology related. As there are well documented guidelines available in this area, it made the application of Hallas to these cases easier (Gallagher et al. 2012). During the in-patient study trial protocols and guidelines for oncology cases were often available and contained information about ADR prevention for example, prevention of chemotherapy induced nausea and vomiting. In contrast, there were no guidelines available for the cardiac related ADRs for example fluid retention, cardiac failure, hyponatremia, or hypokalaemia. There were no clear guidelines available for the prevention of opioid related constipation although some of the treatment protocols referred to constipation and the co-prescription of laxatives the guidance was unclear and varied between different protocols and guidelines. Other examples where no guidelines were available included diarrhoea, hypomagnesaemia, and raised liver enzymes.

The Hallas scale (1990) was used for the ADRIC admissions study but appeared unsuitable for the ADRIC inpatient study owing to difficulties relating to the need to have comprehensive knowledge of the optimal treatment for all conditions represented in the cohort, the need to assess the obligatory demands of a case and the incomplete coverage of guidelines. The ADR cases were divided into four main therapeutic areas surgical, medical, oncology and cardiology and covered a wide range of conditions. For some patients in the cohort their treatment was often guided by multiple specialists. With the lack of guidelines and the wide variation in

cases in order to have used Hallas to assess avoidability in the ADRIC inpatient study it would have required the study team consulting with experts for the specific areas and asking the clinical team involved to provide a rationale for treatment. This would not have been feasible. As a result of this it was decided by the study group that we would design a new AAT which would be more suitable for use in paediatrics by avoiding these difficulties and which could also be used in other settings. Ideally, the newly developed AAT should be generalisable to a variety of different patient groups, reproducible and easy to use.

Hallas is not the only approach that we could have used for the inpatient study. However, other approaches such as Schumock and Thornton (see Figure 1.3) involved similar judgments about appropriate care particularly questions 1 and 2. Therefore, it was decided that the Schumock and Thornton tool was not appropriate for use in the ADRIC in-patient study either.

2.2 Aim and objectives of this work

The aim of this study was to develop a new avoidability assessment tool that was generalisable and met all of the criteria of a good tool as described by Hakkarainen et al. (2012a). The objectives were to develop an algorithm with dichotomous responses based on Hallas (1990) and to conduct reliability/validity testing on the new tool as per Hakkarainen et al. (2012a) recommendations. To assess the avoidability of a selection of ADRs reported in the ADRIC inpatient study and to identify strategies for clinical practice that might reduce the incidence of ADRs.

2.3 Methods

2.3.1 Preliminary Work

A modified version (Figure 2.1) of the Hallas Scale (1990) was used as the starting point for the development of the Liverpool avoidability assessment tool (LAAT) but the focus was on the available information sources. The study team included experienced paediatricians, clinical paediatric pharmacists, a paediatric research

nurse and research methodologists. In discussion, the study team defined a number of principles that would underlie the new tool. The team wanted to ascertain if the relevant information was available in sources that prescribers would be expected to use, and, if so, whether the recommended advice was followed. The intention was to keep the tool as generalisable as possible by asking if accessible management or treatment plans were available. These could be local, national or international. We recommended that only high-quality guidelines were considered. A guideline that would be recognised as appropriate by a reasonable body of opinion for example, Scottish Intercollegiate Guidelines Network (SIGN), National Institute for Health and Care Excellence (NICE), Royal College of Paediatrics and Child Health (RCPCH) or other peer-reviewed guidelines (Brouwers et al. 2010). For example in the case of post-operative nausea and vomiting, examples of appropriate management plans could include: Alder Hey Children's NHS Trust guideline on post-operative nausea and vomiting or the association of paediatric anaesthetists of Great Britain and Ireland (APA) guideline on the prevention of post-operative vomiting in children. As guidelines are not always available, or contain no information on prevention of ADRs, we added other information sources, for example British National Formulary for children (BNF-C), Summary of Product Characteristics (SmPC).

Figure 2.1 Modified Hallas scale

Hallas Scale (Hallas et al. 1990)

- Definitely avoidable: The event was due to a drug treatment procedure inconsistent with present-day knowledge of good medical practice or was clearly unrealistic, taking the known circumstances into account
- Possibly avoidable: The prescription was not erroneous but the event could have been avoided by an effort exceeding the obligatory demands
- Not avoidable: The event could not have been avoided by any reasonable means, or was an unpredictable event in the course of a treatment fully in accordance with good medical practice
- Unevaluable: The data for rating could not be obtained or the evidence was conflicting

Problems

Inconsistent evaluations due to difficulties around the definition of “effort exceeding the obligatory demands of present day knowledge of good medical practice”

Numbers of reactions which are impossible to assess.

Adapted Hallas Scale

Definitely avoidable

- Treatment not used in accordance with relevant source documentation (SPC, BNFC, Local Guidelines or pathway)
- Non-administration of a prophylactic treatment specified in the relevant source documentation which could have been given within a realistic time course

Possibly avoidable

- One or more alternative approaches are found in relevant source documentation
- Prophylactic or mitigating treatment available in theory, but not part of source documentation

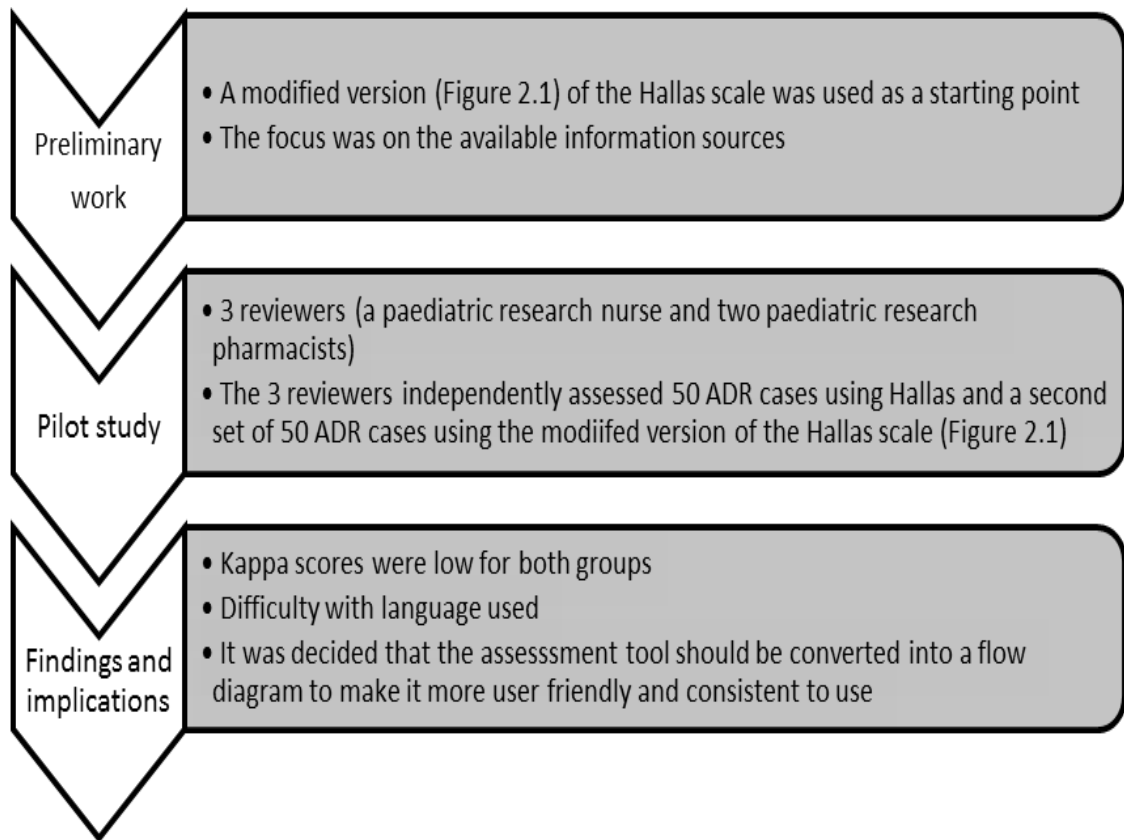
Not avoidable

- Idiosyncratic reaction
 - Anaphylaxis with penicillin in a patient with no previous history of allergy
- Treatment used in accordance with source documentation

Unevaluable

- Lack of information about optimal care (no relevant source documentation)

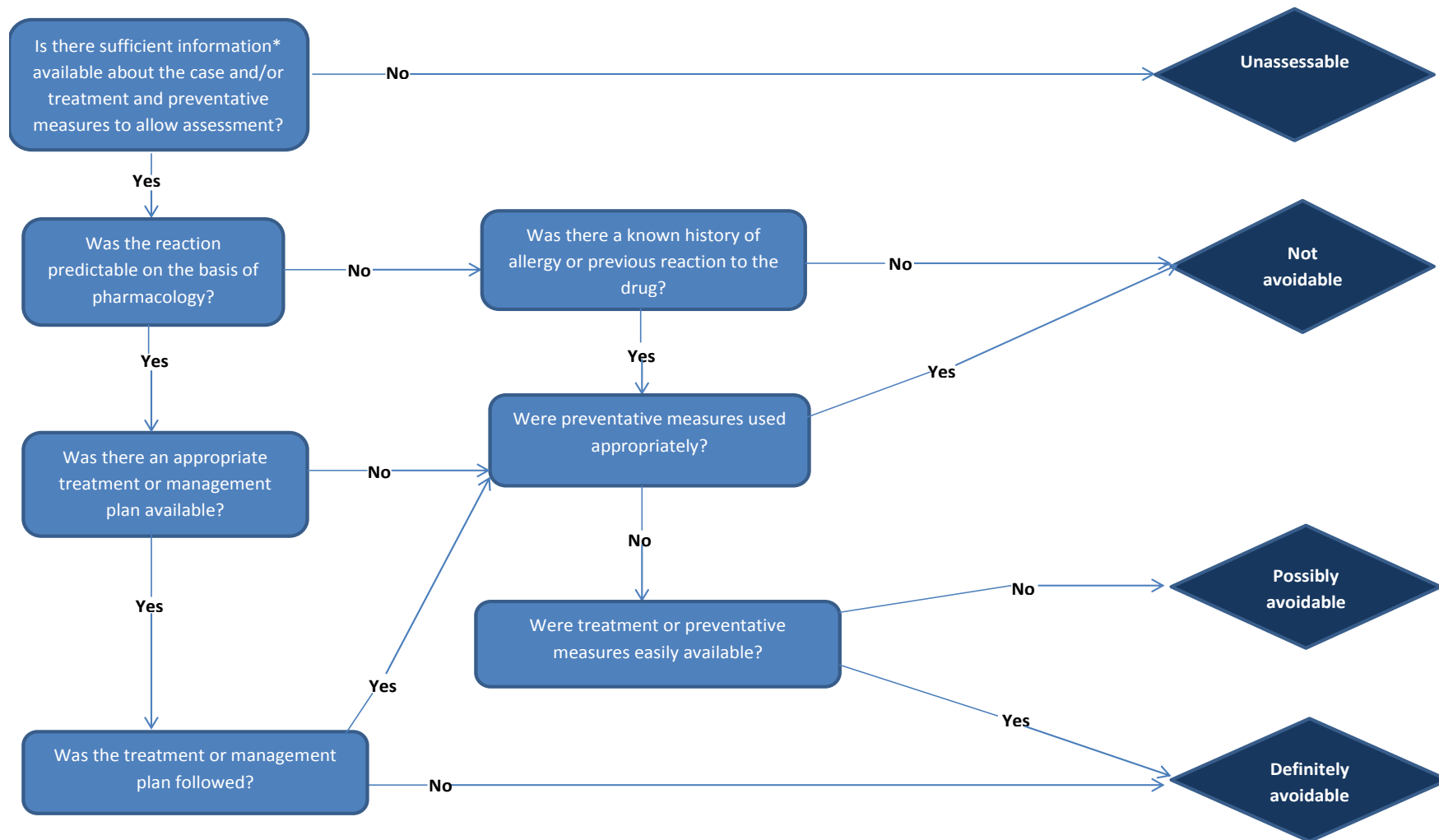
Figure 2.2 Flow chart of the preliminary work on the development of a new AAT



A pilot study was carried out in November 2011, where three reviewers (a research nurse, and two pharmacists, all members of the ADRIC Study team independently assessed fifty ADR cases using a modified version of the Hallas scale (Figure 2.1) and a second fifty cases using the original Hallas scale (1990). The results were compared and inter-rater reliability (IRR) testing was carried out on both groups. Kappa values were interpreted according to the guidance from Altman (1991). The kappa scores for both groups were low. The modified Hallas group scores were poor, with pairwise kappa scores ranging from 0.0597 to 0.159. The kappa scores for the Hallas group were fair with pairwise kappa scores ranging from 0.209 to 0.357. The reason for slightly better kappa scores for the Hallas group may be due to the nature of the cases. The problem appeared to be distinguishing between ‘possibly avoidable’ and ‘not avoidable’. There was difficulty with the language ‘effort exceeding obligatory demands’ and what constituted this.

It was agreed that the LAAT should be redesigned to a flow diagram in an attempt to make it more user friendly and consistent to use. It was decided that some questions required rewording and that this should be done by a consensus approach (Ferner, Aronson 2010b). We achieved consensus by agreement among peers without pre-set criteria and the consensus group was a multidisciplinary team (MDT) comprising a research children's nurse, paediatrician and a paediatric pharmacist. A research pharmacist observed the group process and gathered comments from the participants. The initial tool was modified at each stage based on feedback to improve functionality and remove inconsistencies (see figure 2.3 Version 1 of the AAT). This version of the AAT was fed into the next stage of development.

Figure 2.3 Version 1 of the AAT



* If the case is 'Unassessable' please specify if this is due to "lack of information about the case" or "lack of information about guidance"

2.3.2 Development of the LAAT

Phase 1a: Define the tool

It was agreed that the best way to develop a new tool was to take a consensus approach in reviewing ADR cases. The format of the new tool was a flow diagram with dichotomous responses to each question followed by a routing to the next relevant question (see Version 1 of the tool, Figure 2.3, which had been developed in preliminary work). It was decided this would differ from the specific criteria that Hallas et al. (1990) has for each avoidability category. Initially twenty cases (randomly selected) from the ADRIC inpatient study were reviewed to define the tool (see Appendix 1 for a sample ADR case). This was carried out by a MDT working together to discuss clinical practice and avoidability outcome and observed by a research pharmacist. It was an iterative process and each question in the newly modified avoidability flow diagram was reviewed by the investigators during the consensus meetings and any necessary changes were made (see figure 2.4 for the LAAT development process). Two out of twenty cases were classified as 'unassessable' because of lack of information about the case. Both were constipation cases and were missing vital information, such as fluid balance charts making the cases unassessable.

The MDT carried out an avoidability assessment on the twenty cases. 20% of the ADRs were categorised as either 'possibly' or 'definitely avoidable', 70% of ADRs were deemed 'unavoidable' and 10% were 'unassessable'. It was felt that it was not appropriate to distinguish between guidelines, and, for the purpose of the ADRIC inpatient study cases, we accepted, any available guidance based on an acceptable body of opinion, for example SIGN, Alder Hey Trust guidance or NICE guidance. A glossary was prepared to further explain this and other terms (see Appendix 2). Any areas of disagreement or discrepancies were reviewed by a clinical pharmacologist, who also reviewed the iterations as they moved through the various stages of development.

The consensus group discussed the different levels of avoidability and came up with the following list:

- **Patient** (vital source of information)
- **Ward** (communication/handover/feedback)
- **Departmental** (management plans for chronic patients/staff training)
- **Institutional** (what guidelines are in place and how up to date are they?/electronic prescribing (EP)/root cause analysis (RCA)/audit)
- **Professional** (Continuing professional development (CPD)/training/over the counter (OTC) medicines)
- **National** (guidelines/standards/regulatory systems/off-label/unlicensed prescribing)

Phase 1b: Modify the tool

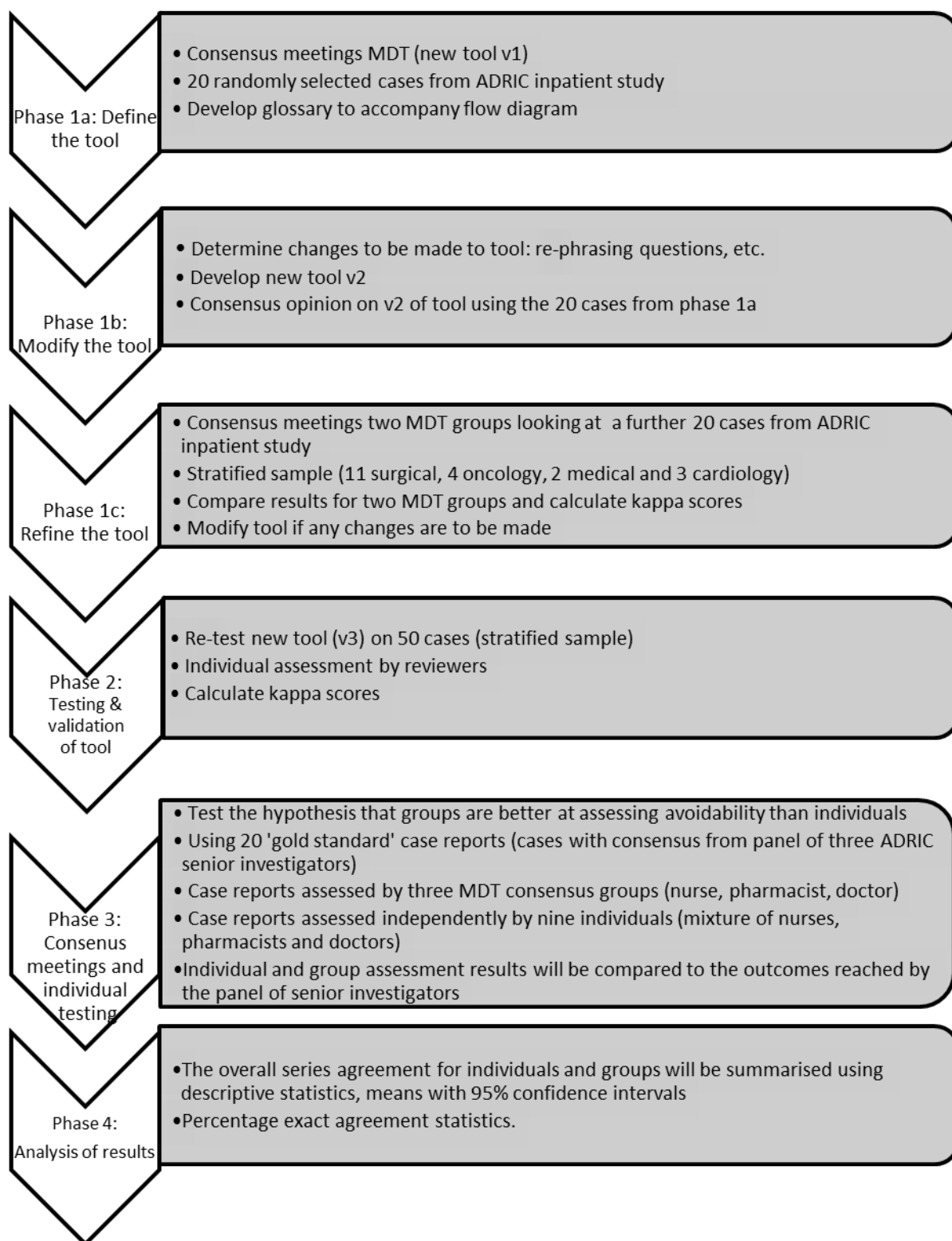
The flow diagram was modified using twenty randomly selected cases from ADRIC inpatient study, with rephrasing of questions and additional information sources. Consensus of opinion was reached for the design and this version of the tool (Figure 2.4) was carried forward to the next phase.

Phase 1c: Refine the tool

Two MDT groups, the original plus a new group (paediatric nurse, pharmacist and paediatrician), reached consensus about a second set of twenty cases from the ADRIC inpatient study, which were a randomly selected stratified sample in order to reflect the breakdown of specialties and types of ADRs in the study. The breakdown of the probable and definite cases was as follows:

- 11 surgical
- 4 oncology
- 2 medical
- 3 cardiology

Figure 2.4 Flow chart of the development of the Liverpool ADR avoidability assessment tool



Probable and definite cases were selected in line with the analysis undertaken in the ADRIC inpatient study and therefore possible cases were not included in the ADR case selection (Thiesen et al. 2013). Both groups reviewed the same twenty cases. The results were compared, kappa scores were calculated and the concordance of routes and the final avoidability categories assigned. Both MDT meetings were observed and the assumptions and approaches of the teams were recorded. The difference in approach taken by the two MDTs was interesting with the original MDT looking up more guidelines than the second MDT despite the same resources being available to both groups. The latter approach may be more reflective of what happens in clinical practice. The second MDT group classified 3/20 cases as 'unassessable' whereas the other group assessed all 20 cases (see Table 2.1 for details of the cases). Further changes to the tool were made as a result of the findings with two of the questions being amended to include 'known preventative strategies'- prophylactic or concomitant medicines or any necessary monitoring. This was due to the three constipation cases in the stratified sample which the groups disagreed on, with one group categorising the cases as either 'possibly' or 'definitely avoidable' and the other categorising all three cases as 'not avoidable'.

This led to a change in two questions on the tool (see Figure 2.5 and 2.6 – amended questions are circled):

'Was there an appropriate treatment or management plan, with information about the ADR and its avoidance, available?' was changed to *'Were there known preventative strategies and/or appropriate management plan(s), with information about ADR avoidance available?'*

The second change was to *'Was the drug(s) used in accordance with the treatment or management plan?'* which was amended to *'Were the strategies and/or management plan(s) followed?'*

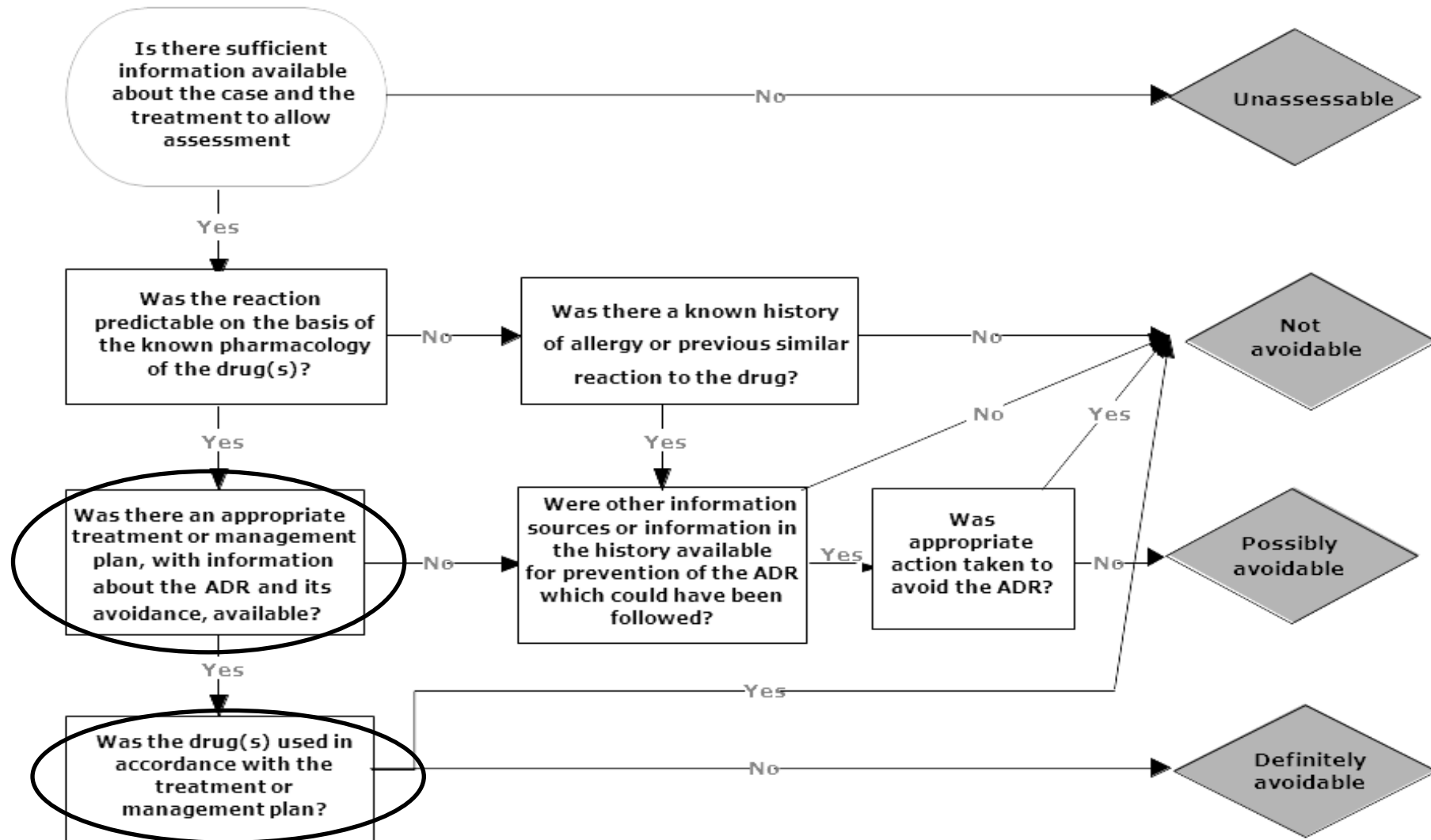
These changes were to allow for ADR cases where either, there is no management plan available or, there is a management plan available but it contains no reference about ADR avoidance but preventative strategies may be applicable; for example the constipation cases.

Table 2.1 Details of the cases categorised as unassessable by MDT 2 in phase 1c

ADR Type	Drug (s) involved in ADR	Causality	Avoidability	Rationale
Drug withdrawal syndrome	Chloral Hydrate	Probable	Unassessable	Lack of information about the case - query other reasons for patient being unsettled. More information needed to assess.
Hypotension	Clonidine 1mcg/mL & Levobupivacaine 1.25mg/mL	Probable	Unassessable	Lack of information about the case - need information about intra-op blood loss and fluids given to assess the case.
Hypertension	Methylprednisolone	Definite	Unassessable	Lack of information about the case - would like additional information regarding rates of infusion and more frequent BP measurements.

Figure 2.5 Version 2 of the avoidability assessment tool (used in Phase 1c)

Version of the tool used in Phase 1c



2.3.2 Phase 2: Testing and validation of the tool

The refined tool (version 3, Figure 2.6) was then tested on a further set of ADRIC inpatient study cases with the aim being to improve inter-rater reliability (IRR). This phase involved the assessment of fifty cases by six individual reviewers using the newly refined tool. For further details on completing an avoidability assessment see the accompanying glossary and guide to the questions in the tool (Appendix 2). These 50 cases were a stratified sample of possible, probable and definite cases (26 surgical, 9 oncology, 9 medical and 6 cardiology). The reviewers included two nurses (HM and JS), two pharmacists (JB and LB) and two paediatricians (DH, MT). These cases were assessed in terms of pairwise agreements between the investigators. Cases where extreme disagreement occurred i.e. where the avoidability assessment differed by more than one category for example 'not avoidable' and 'definitely avoidable' and any cases for which half of the raters differed in assigning a category were identified and the questions which caused the discrepancies were reviewed.

2.3.3 Data analysis

The results were presented as categorical scores from the newly developed tool and inter- rater agreements were calculated using kappa scores with 95% confidence intervals (CI). Pairwise kappa scores were compared with global kappa scores. The percentage extreme disagreement (%ED) where the avoidability scores between two raters of the same case are wider than one interval apart were calculated to measure extreme disagreement between pairwise kappa scores. Pairwise kappa scores were also calculated by speciality to investigate the differences between surgical, medical, oncology and cardiology cases.

Kappa values were interpreted according to the guidance from Altman (1991) (Table 2.2) (Altman 1991):

Table 2.2 Interpreted kappa values according to Altman (1991)

Agreement	Kappa
Poor	< 0.2
Fair	0.21–0.40
Moderate	0.41–0.60
Good	0.61–0.80
Very good	0.81–1.00

There was no preset level for Kappa acceptability for the development of the LAAT. It may have been useful to have assigned a minimum Kappa score for agreement.

2.4 Results

2.4.1 Phase 1c

The assessment of 20 ADR cases was undertaken by two different MDT groups (Table 2.3) using LAAT version 2 and showed fair agreement with a kappa score of 0.29 (95% CI -0.04 to 0.62). The two groups agreed on 65% of the ADR cases. Group members commented that a mixture of professions was needed to give a full assessment of avoidability. Changes to the tool were made as a result of the findings, with two of the questions being amended to include 'known preventative strategies'.

Figure 2.6 The Liverpool ADR avoidability assessment tool (LAAT) (version 3 as used in Phase 2)

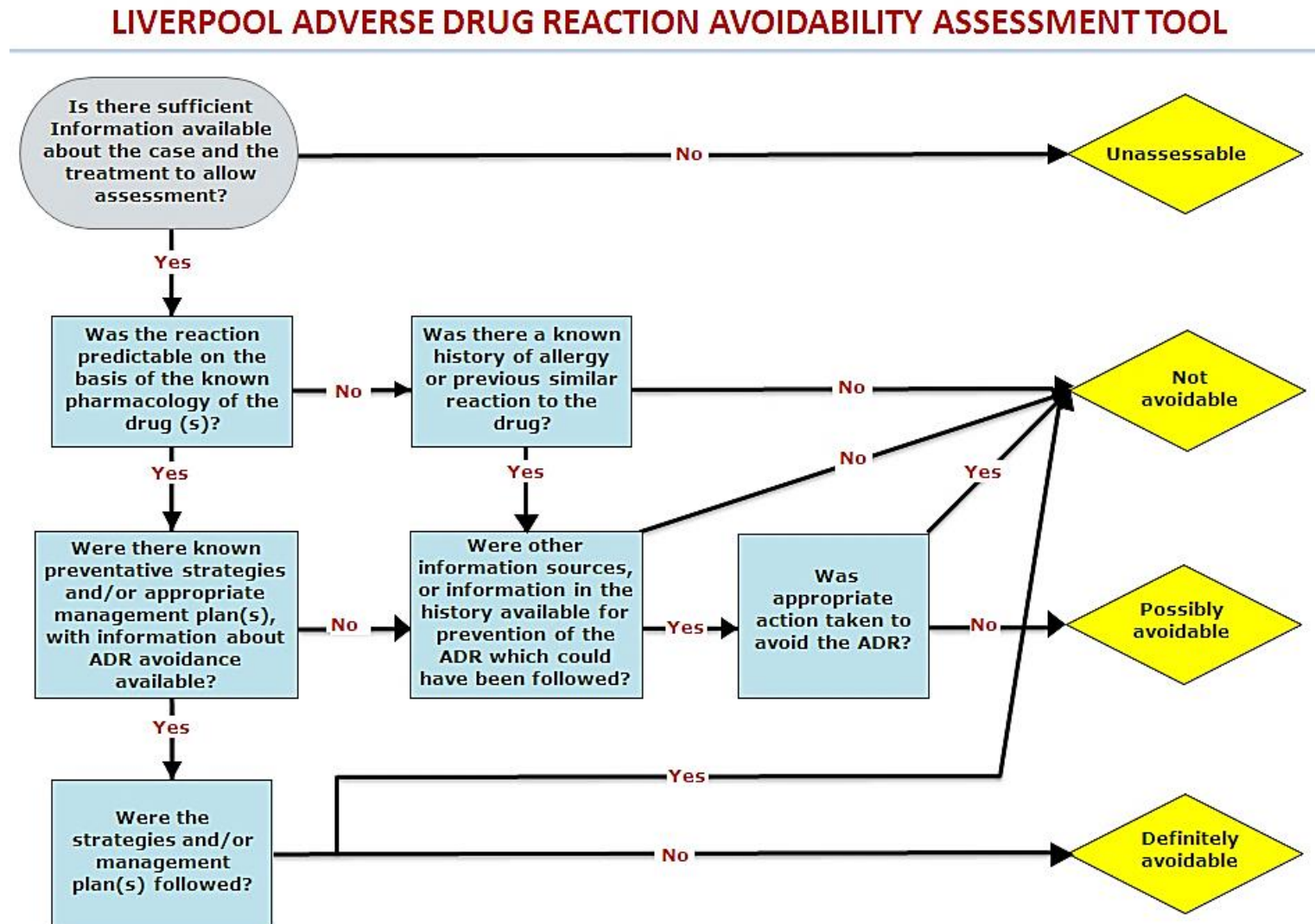


Table 2.3 Phase 1c results - ADR type and avoidability outcome

ADR Type	MDT 1 - avoidability outcome	MDT 2 - avoidability outcome
Surgical		
Diarrhoea	Not avoidable	Not avoidable
Procedural vomiting	Not avoidable	Not avoidable
Constipation	Possibly avoidable	Not avoidable
Constipation	Definitely avoidable	Not avoidable
Urinary retention post-operative	Not avoidable	Not avoidable
Constipation	Possibly avoidable	Not avoidable
Hypotension	Not avoidable	Unassessable
Somnolence	Not avoidable	Not avoidable
Somnolence	Not avoidable	Not avoidable
Procedural vomiting	Definitely avoidable	Definitely avoidable
Drug withdrawal syndrome	Possibly avoidable	Unassessable
Medical		
Hypertension	Not avoidable	Unassessable
Hypomagnesaemia	Not avoidable	Not avoidable
Cardiology		
Procedural vomiting + Vomiting	Definitely avoidable	Definitely avoidable
Hypotension	Not avoidable	Not avoidable
Melaena	Not avoidable	Not avoidable
Oncology		
Nausea	Not avoidable	Not avoidable
Vomiting	Definitely avoidable	Not avoidable
Pain	Not avoidable	Not avoidable
Hypokalaemia	Not avoidable	Not avoidable
Overall results	MDT 1	MDT 2
Unassessable	0 (0%)	3 (15%)
Not avoidable	13 (65%)	15 (75%)
Possibly avoidable	3 (15%)	0 (0%)
Definitely avoidable	4 (20%)	2 (10%)
Total	20	20

2.4.2 Phase 2

Six individual reviewers assessed 50 ADR case reports using version 3 of the LAAT. Pairwise kappa scores ranged from poor to good, 0.12 to 0.75 and percentage exact agreement (%EA) ranged from 52-90% (Table 2.4). 77% of cases were categorised as 'not avoidable' and 23% were classified as either 'possibly' or 'definitely avoidable' (Table 2.5). Stronger agreement was found within professions than between professions. Comparison of reviewers by specialty type highlighted that agreement was better for certain specialties particularly oncology and surgical. In 34% of all cases all six reviewers agreed on the avoidability assessment and this increased to 68% for five reviewers. Agreement was better between the ADRIC study group team (HM, JB and LB). Some of the comments recorded for the cases with disagreement included: 'no relevant experience in area', 'no access to the relevant guideline' and 'unsure if this is even an ADR'; which perhaps underpins the need for a MDT to carry out the assessments. Or, if assessments are to be carried out individually this highlights the need for information or guidance on assessments to be provided.

Table 2.4 Avoidability assessment of ADR cases from phase 2

		Assessor 2						
			LB	JB	HM	MT	JS	DH
Assessor 1	LB	% EA		90%	84%	78%	60%	70%
		Kappa (95% CI)		0.75 (0.53 to 0.97)	0.60 (0.42 to 0.79)	0.49 (0.26 to 0.72)	0.23 (0.07 to 0.38)	0.34 (0.11 to 0.56)
	JB	% EA			80%	68%	60%	60%
		Kappa (95% CI)			0.49 (0.31 to 0.67)	0.26 (0.05 to 0.46)	0.20 (0.03 to 0.37)	0.12 (-0.09 to 0.32)
	HM	% EA				70%	66%	64%
		Kappa (95% CI)				0.30 (0.12 to 0.49)	0.32 (0.17 to 0.47)	0.21 (0.03 to 0.39)
	MT	% EA					58%	62%
		Kappa (95% CI)					0.23 (0.08 to 0.38)	0.20 (-0.02 to 0.42)
	JS	% EA						52%
		Kappa (95% CI)						0.18 (0.03 to 0.33)
	DH	% EA						
		Kappa (95% CI)						

%EA - Percentage Exact Agreement

Kappa Scores

Agreement	Kappa
Poor	< 0.2
Fair	0.21–0.40
Moderate	0.41–0.60
Good	0.61–0.80
Very good	0.81–1.00

Reviewer Key

Initials	Reviewer Type	Member of ADRIC
LB	Research Pharmacist	Member of the ADRIC study team
JB	Research Pharmacist	Member of the ADRIC study team
HM	Research Nurse	Member of the ADRIC study team
MT	Paediatrician	Member of the ADRIC Senior Investigator group
DH	Paediatrician	No
JS	Nurse (Pain team)	No

Kappa values were interpreted according to the guidance from Altman (1991)

Table 2.5 Possibly and definitely avoidable cases and explanation of assessment result

ADR Type	Frequency	Avoidability assessment	Drug Classes	Rationale for potential avoidability
Procedural vomiting	3	Definitely	Drugs used in general anaesthesia, Opioid analgesia	Appropriate prophylaxis not used
Vomiting	1	Definitely	Cytotoxics	Appropriate prophylaxis not used
Constipation	5	Definitely	Opioid analgesia +/- Drugs used in nausea	Appropriate prophylaxis not used
Procedural vomiting & vomiting	1	Definitely	Drugs used in general anaesthesia, Opioid analgesia	Appropriate prophylaxis not used
Constipation	1	Possibly	Opioid analgesia	Appropriate prophylaxis not used

2.5 Discussion

There have been many attempts to devise tools or scales to help determine avoidability. There is currently no standardised method for determining ADR avoidability and many of the established tools are not suitable for use in paediatric practice. The available instruments for assessment of avoidability of ADRs vary in reliability and validity (Smyth et al. 2012). The assessment of avoidability is compromised by a lack of consensus on the definition of avoidability and associated heterogeneity in underpinning methodology for instrument development. No instruments were available specifically for characterisation of ADRs in children and young people, and therefore there was a requirement to develop such instruments (Smyth et al. 2012). The LAAT was an attempt to develop and validate a new instrument to improve the assessment of avoidability of ADRs in children.

The new AAT was developed for use in hospital settings by healthcare professionals involved in clinical care. Our immediate need was for a research tool that would be used to assess the avoidability of cases described prospectively using structured data collection instruments. Whilst it may be useful in a research setting to know whether an ADR is 'possibly' or 'definitely' avoidable; in clinical practice it is not really important to distinguish between the two. As when an ADR is categorised as possibly or definitely avoidable the end result and impact to the patient is ultimately the same. The action taken and the learning points or system changes which may be implemented as a result to minimise the risk of recurrence are the same; regardless of whether the ADR was possibly or definitely avoidable. ADRs categorised as avoidable should be treated in the same manner. If anything can be done to potentially avoid the ADR these steps should be taken regardless of the assigned avoidability category. The four avoidability categories were maintained on the LAAT to allow direct comparison to the ADR cases assessed using the Hallas scale. If the LAAT was to be further developed for use in a clinical setting the number of categories could be reduced to 'avoidable' and 'not avoidable'. In the context of a clinical tool the "unassessable" category also becomes less relevant. As

when an ADR is categorised as “unassessable” it may be indicative that something was missed or not completed in the care of the patient. However a small number of “unassessable” cases in the research setting may have been due to information missing from the medical notes which was required for the completion of the ADR case report. It would be important to distinguish between those possibilities in further development of the LAAT in a clinical context. The ADR case reports for the ADRIC study were written using the medical notes, fluid balance charts, prescription charts, nursing notes on the inpatient system Meditech were also viewed and information added to the report where appropriate. The ADRIC study team endeavoured to include all relevant information where available. Occasionally, some information was missing for example fluid balance charts were not routinely kept by all wards. Table 2.1 shows the details of cases deemed “unassessable” by one of the MDTs in Phase 1c. If ADR avoidability assessments were conducted prospectively it may reduce the number of “unassessable” cases. The advantage of assessing avoidability using the ADRIC case reports was that it significantly reduced the amount of time taken to assess the case as the ADR case reports contained the information required to make the assessments rather than asking reviewers to search through the medical notes which may not have been feasible given the time constraints. The prospective avoidability assessments using medical notes may be more time consuming; depending on the team assessing the case and their familiarity of the patient which, in some cases may make the process quicker if they are very familiar with the patient’s history.

If the LAAT had been designed for a clinical context it might have looked quite different. The number of avoidability categories could have been reduced down from four to two: ‘avoidable’ and ‘not avoidable’ for the reasons discussed above. This may have resulted in a tool that was less complex and perhaps easier to use. The reduction in the number of avoidability categories from four to two is likely to have improved inter-rater reliability as the number of variables would be reduced”. However, as the LAAT was designed as a research tool rather than a clinical tool the four avoidability categories used in the Hallas scale were maintained in the LAAT.

We anticipate that the tool will also be used to assess cases described retrospectively. For example, to summarise the investigation of high impact or sentinel cases during safety review by a medicines management committee.

The results of the initial validation studies showed mixed IRR, which prompted a review of the appropriateness of the tool and its questions. A central theme of the review was the finding that the assessment of avoidability frequently required information or judgments that were not part of the routine expertise of particular professions. A comprehensive assessment required input from multiple professionals. It was thus hypothesised that MDT groups may be more consistent than individuals as groups are more representative of the ward setting where care is provided within teams. This gave rise to the next step in the development of the LAAT: to test the hypothesis that group assessments are superior to individual avoidability assessments.

Following the completion of Phase 2 it was decided that further testing was needed and that perhaps the best way to assess avoidability is in a group setting. Pairwise kappa scores ranged from poor to good agreement; possible reasons for this may be due to lack of experience in certain specialty areas or a possible training effect. As mentioned in the Methods Section 2.3 it may have been useful to have assigned a minimum Kappa score for agreement. As the LAAT was designed as a research tool rather than a clinical tool the minimum value for Kappa might have been set at a lower value than if the LAAT was designed as a clinical tool. For a clinical tool the minimum Kappa score might be set to a minimum of 0.80 which indicates good agreement according to Altman (1991) and for the LAAT it might be more reasonable to set a lower Kappa of 0.60 which indicates moderate agreement. A higher Kappa of 0.80 may not be realistic for the LAAT given the complex nature of avoidability assessments; depending on the expertise of the reviewers conducting the assessments. In any future testing of the LAAT or in re-development of the LAAT into a clinical tool for assessing ADRs *“a priori”* Kappa value of 0.6 could be set for the minimum level of agreement for reviewers.

The next stage in the development process will be to carry out group assessments of additional cases and look for an improvement in the results. This further testing in a group setting is required to develop and validate the tool. This is discussed in Chapter 3.

We have conducted preliminary testing of the LAAT, it has face validity and is easy to use. However, a number of issues were raised. These include the dependence on guidelines and variations in clinical practice. In phase 2, comparison of reviewers by specialty type highlighted that agreement was better for certain specialties particularly oncology and surgical. Unlike the Hallas score; using the LAAT to assess POV case proved relatively straightforward due to the nature of the questions on the LAAT particularly 'were there known preventative strategies and/or appropriate management plan(s) with information about ADR avoidance available. The assessor was able to consult the available guidelines to answer the questions on the LAAT rather than being expected to know or consult the literature on the most appropriate type of anaesthetic and analgesia for a particular patient and a particular operation.

This may be explained by the number of guidelines available in these areas. Many oncology cases have detailed protocols and treatment regimens although the level of detail varies amongst different protocols. Also, it became apparent that despite guidelines being available for some cases not all reviewers consult them. Some cited guidelines from memory correctly or incorrectly and some clinicians used experience or prior knowledge to assess the cases. The subtlety in definitions between prevention, management and amelioration of ADRs caused confusion with reviewers at times with the ADRIC study team appearing to have a good understanding of the differences. Agreement was stronger between the ADRIC study group team (HM, JB and LB). This raised the question of reviewer's experience of ADR assessments and ultimately who is likely to use the tool. The LAAT is predominantly a research tool designed for use in the assessment of ADRs rather than a clinical tool per se. Reviewer type and experience of the assessor was also

found to affect the results and the way in which the tool was interpreted. In the systematic review by Hakkarainen et al. (2012a) the avoidability assessment was made by physicians in 60% of the articles and by pharmacists in 29%, and often a combination of them both. In 20% of the articles, the assessors were described as trained for, or experienced in, conducting avoidability assessments (Hakkarainen et al. 2012a).

It may not be possible to define a generalisable tool, but it may be possible to define a tool that individuals can use consistently. However, the tool in itself may not be sufficient to develop consistent results between individuals or across settings. Consistent results may require a standard body of guidelines, or gold standards for acceptable care. Consistent results may require clinical experience relevant to the suspected ADR. Nevertheless, the tool may provide useful insights within an individual setting. A limitation of this study was the number of cases assessed in the different phases with 20 cases being used for some phases. This was due to the feasibility of assessments and the time taken for MDT meetings. The next step in the development process will be to investigate if group assessment improves agreement and reliability (Chapter 3).

Hakkarainen et al. (2012a) have made some useful suggestions for future research, which we followed. They recommended that future studies include reliability and validity testing; take action to standardise the measurement process; provide information on the assessors in terms of training and experience in assessing avoidability; and describe how the assessments took place (i.e. whether cases were assessed independently or via consensus and how any disagreement is dealt with). They also stated that owing to the limitations and diversity of assessments it remains unknown if variation in avoidability rates in different settings and populations is due to the methodology used or actual differences in avoidability rates. They suggested that there is a need for modifying previous instruments or developing new ones for use in different settings, and that a starting point for developing a new instrument could be to begin with a clear definition for the

avoidability of different types of ADEs. They also recommended that any newly developed instruments should be compared with existing ones and that if one or more instrument gained rigorous evidence and became a gold standard it would facilitate comparisons of different studies (Hakkarainen et al. 2012a). The development of the LAAT followed these recommendations. Chapter 5 of this thesis describes the comparison of the LAAT to Hallas (1990) for the assessment of the ADRIC admissions study ADR case reports (Gallagher et al. 2012).

2.6 Conclusion

Avoidability assessment is feasible but needs careful attention to methods. The ADRIC systematic review (Smyth et al. 2012) highlighted the lack of avoidability data in paediatric ADR studies and the need to develop paediatric specific tools. We have developed the LAAT which showed mixed IRR in the individual assessment phase; therefore, further testing in a group setting is required to develop and validate the tool.

Chapter 3: Consensus meetings and individual testing

3.1 Introduction

Consensus is defined as '*general agreement*' or '*the judgement arrived at by most of those concerned*' (Meriam Webster).

'Consensus is only one step beyond individual judgement it is possible for experts to agree and yet be wrong' (Ferner, Aronson 2010b).

As noted in Chapter 2 group assessment may be a way to improve the assessment of avoidability of ADRs. Here we consider ways in which groups could assess the avoidability of ADRs using the LAAT. While the LAAT was initially designed as a research tool, the intention was that it could also be used within clinical practice. Accordingly, our choice of method for group work needed to account for the demands of the "real world" as well as the research world.

Consensus decision-making is a process used by groups seeking to generate widespread levels of participation and agreement. Consensus methods can also deal with conflicting scientific evidence (Murphy et al. 1998b). The aim of consensus methods is to determine the extent to which experts or lay people agree about a given issue (Jones, Hunter 1995). They range from formal to informal methods. The vast majority of collective decisions in healthcare are based on group meetings, such as committees, which have been largely unstructured with few formal rules or procedures (Murphy et al. 1998b). In general, consensus methods aim to enhance decision-making, synthesise expert opinion or provide some means of measurement where there is incomplete evidence or uncertainty (Jones, Hunter 1995). Consensus work can also lead to buy-in when action must be taken despite imperfect evidence. There are three main types of formal methods for consensus development: Delphi method, Nominal group technique (NGT) and Consensus development conference. The research question and the planned model of participant interaction generally determine the method chosen. For example,

nominal group techniques are used initially to generate and then prioritise ideas, while the Delphi technique involves two or more postal or electronic rounds of questionnaires to prioritise predetermined categories (Campbell, Cantrill 2001). Consensus development conferences involve face-to-face discussion and debate between stakeholders (Halcomb, Davidson & Hardaker 2008).

Delphi method: The Delphi method was developed by the Rand Corporation in the 1950s and the aim was to synthesise expert opinion (Black et al. 1999). It has been used for a variety of purposes in the health care sector. Participants never meet or interact directly. Instead they are sent questionnaires and asked to record their views. The method has been criticised for diminishing the potentially positive aspects of interaction in the face-to-face meetings (Black et al. 1999). The Delphi process is a survey technique for decision-making among isolated respondents. On balance the Delphi method was not suitable for our study as experience shows that group interaction and discussion are valuable during the assessment of an ADR for avoidability.

NGT: NGT was developed in 1971 by Delbecq and Van de Ven in the context of committee decision making (Black et al. 1999). The aim of NGT is to structure interaction within a group. Firstly, each participant is asked to record his or her ideas independently and privately. The ideas are then listed in a round-robin format. Each idea is then discussed in turn by the group; a facilitator oversees the process. The facilitator should be an expert on the topic for discussion, or a credible non-expert (Black et al. 1999). They ensure all participants have the opportunity to express their views and it reduces dominance by individuals. Conducting NGT is an efficient process for the participants. However, the data analysis, particularly the qualitative aspect, is a time consuming process due to the volume of information produced. On balance NGT was not suitable for our study as it would not be practical in real-world settings.

Consensus development conference: a selected group of about ten people is brought together to reach consensus about an issue. Most suggest that participants should ideally be experts in the field and have credibility with the target audience (Black et al. 1999, Halcomb, Davidson & Hardaker 2008). According to Black et al. (1999) the effect of heterogeneity on group decision-making can lead to a better performance; but there is also some evidence to suggest it could have an adverse effect as conflict may arise between the diverse group. Conference participants come together in an open meeting to hear evidence from various stakeholders or experts in the field who are not members of the decision making group (Black et al. 1999). After hearing the evidence participants consider the key questions in the light of the evidence presented and attempt to reach consensus and produce a consensus statement (Black et al. 1999). A key advantage of the consensus development conference method is that it fosters dialogue, debate and discussion between participants (Halcomb, Davidson & Hardaker 2008). The development of consensus conferences has drawn on aspects of judicial decision-making. Although this method was developed from a need to make decisions in the public forum, rather than a response to research on group decision-making techniques, it has mostly been evaluated in terms of its decision making properties. On balance consensus development conference was not suitable for our purposes due the large number of participants required that would not be realistic in real practice.

None of the available formal methods were suitable for our study because the target users of this tool do not work in large groups. Accordingly we elected to use an informal method that drew on some elements of the formal methods. The tool was designed for use in real-world clinical settings. Hence the consensus method chosen should be applicable in real-world settings.

The main characteristic of the informal method was small MDT groups. Each group had 3 reviewers including nurse, pharmacist and doctor with experience of prescribing, administering, or dispensing medicines for children. It was anticipated that the small groups would work informally in line with standard practice that does

not include formal group processes. Accordingly, the evaluation was designed to measure the outcomes, and process, of informal group work.

An alternative would have been to introduce formal group process and the LAAT. However, it was decided against this, as it would make it difficult to assess the impact of the LAAT because participants would be exposed to two novel things at the same time. Assessment of the LAAT was framed by a descriptive study of informal group process this is described in detail in Chapter 4.

There are no clear guidelines to assist in optimal composition of consensus groups (Black et al. 1999). Campbell and Cantrill suggest that participants reflect the stakeholder group (Campbell, Cantrill 2001). Group composition is an important consideration. In judgements of clinical appropriateness, the most relevant background factor is medical speciality (Jones, Hunter 1995). Generally, having more group members will increase the reliability of a group judgement. However, where the group interacts, large groups may cause coordination problems within the group. It seems likely that below six participants, reliability will decline quite rapidly, while above twelve, improvements in reliability will be subject to diminishing returns (Murphy et al. 1998a).

It was decided that our consensus groups should include a nurse, pharmacist and doctor. During the earlier stages of tool development it was found that including members of each of the three professions accounted for different perspectives and overcame lack of knowledge or areas of uncertainty within each profession. In terms of the feasibility of assessing a larger component of the ADRIC inpatient study cases in the future a smaller group size of three people was decided upon, also this was more representative of other ADR study teams in research who may perhaps be the end-users of the LAAT. Although Murphy et al. (1998a) suggest a group size of between six and ten participants this would not have been practical for this study. Fink et al. (1984) have reported that the number of participants is dependent on the particular type of consensus method being used and is also constrained by the resources available for the individual project (Fink et al. 1984). The number of

stakeholder groups requiring representation may also influence the group size (Halcomb, Davidson & Hardaker 2008). The consensus groups selected for this study included nurse, doctor and pharmacist representation. The quantitative evaluation of the consensus groups was supplemented by an ethnographic approach. Details of this are described in Chapter 4. Ethnography is '*the study of social interactions, behaviours and perceptions that occur within groups*' (Reeves, Kuper & Hodges 2008). Qualitative methods have become increasingly popular in healthcare research in recent years (Britten 2005). Ethnography can generate rich and detailed accounts of clinicians' professional and inter-professional relationships (Reeves, Kuper & Hodges 2008).

3.2 Aim and Objectives

3.2.1 Aim

To test the hypothesis that group avoidability assessments are superior to individual avoidability assessments.

3.2.2 Objectives

To determine:

1. The extent to which individual and group assessments agree with the assessments made by the panel of ADRIC senior investigators.
2. The extent to which agreement between groups is similar to agreement between individuals.

The following explanatory analyses were conducted.

3. Exploration of the factors that influenced decision making in a MDT consensus group.
4. Nature of the areas of disagreement.

3.3 Study Description

3.3.1 Study Design

An observational study comparing the findings reported by assessors assigned to group or individual participation in a retrospective review of selected ADR case reports from the ADRIC inpatient study.

3.3.2 Study Setting

A paediatric tertiary referral centre in the UK.

3.3.3 Sample size and selection of cases

ADR cases

A purposive sample of 25 ADR case reports was selected from the 1446 cases categorised as probable and definite ADRs in the ADRIC inpatient study to reflect different ADR types and avoidability classifications. ADRIC Senior Investigators, clinical pharmacologist (MP), paediatrician (MT) and pharmacist (AN), assessed the cases and reached consensus about avoidability status on the LAAT. This was recorded as the 'gold standard' (GS). Following the first 'gold standard' consensus meeting it was decided that a stratified sample (surgical, medical, cardiology and oncology cases reflecting the breakdown of ADRs) was not appropriate as it falsely magnified agreement. It was therefore important to ensure the ADR cases were independent of each other. It was decided that a highly selective purposive sample based on ADR type and avoidability classification was required. This involved pre-screening of the cases by LB to check for a spread of avoidability classifications (not avoidable, possibly avoidable, and definitely avoidable). The cases were all assessed as probable or definite ADRs using the final causality classification assigned in the study (Thiesen et al. 2013).

Definition of 'gold standard' for each ADR

A panel of two to three ADRIC senior investigators met to define the avoidability status of ADRs to be used in the study on two separate occasions. The meetings were observed; the outcomes and any notes provided on the rationale provided were recorded. The meetings considered a sample of 25 ADR case reports from the ADRIC inpatient study in order to develop a sufficient number of cases for use in the study. Initially a stratified sample was selected as per the previous phases but it was then decided that a purposive sample based on the ADR type was more appropriate in order to fully test the tool. As the stratified sample contained several of the same ADR types such as post-operative nausea and vomiting (PONV) and pruritus cases, it was felt that these cases were not independent of each other and could magnify the appearance of agreement. It was important to make sure that the tool was being validated rather than people's level of agreement on being able to interpret a guideline or pathway. From the sample of 25 cases with a 'gold standard' assessment, 20 were selected for the study in order to maximise the variety of gold standard assessments: see table 3.1 for details of the cases.

Table 3.1 Selected ADR case reports for the study with ‘gold standard’ outcomes

ADRID	ADR Type	Suspected Medicine	Causality	Gold Standard avoidability outcome
1554	Vomiting	Cytarabine	Definite	Definitely avoidable
383	Procedural vomiting	Morphine Sulphate	Probable	Definitely avoidable
138	Somnolence	Codeine Phosphate	Probable	Definitely avoidable
2103	Immunosuppressant drug level increased	Tacrolimus	Probable	Definitely avoidable
1294	Constipation	Fentanyl citrate	Probable	Definitely avoidable
630	Hallucination	Morphine Sulphate	Probable	Not avoidable
2105	Cardiac failure	Bisoprolol fumarate	Definite	Possibly avoidable
293	Respiratory depression	Morphine sulphate	Definite	Possibly avoidable
2015	Flushing	Dexamethasone	Definite	Not avoidable
252	Pruritus	Fentanyl & Levobupivacaine	Probable	Not avoidable
2258	Visual disturbance	Morphine sulphate	Probable	Not avoidable
9	Diarrhoea + Excoriation	Cefotaxime	Probable	Not avoidable
1518	Hypocalcaemia + Hypophosphataemia	Pamidronate	Probable	Not avoidable
2815	Haematemesis	Aspirin	Probable	Not avoidable
477	Hypertension	Prednisolone	Probable	Not avoidable
2844	Infusion associated reaction	Rituximab	Probable	Not avoidable
1224	Urinary retention	Morphine	Definite	Not avoidable
1263	Clostridium difficile colitis	Teicoplanin	Definite	Not avoidable
493	Stomatitis	Clofarabine	Probable	Not avoidable
1572	Hypoglycaemia	Insulin detemir	Probable	Possibly avoidable
Breakdown of avoidability categories				
Definitely avoidable		5		
Possibly avoidable		3		
Not avoidable		12		
Total		20		

3.4 Methodology

Participants were assigned either to assess a selection of ADR cases reports independently or to one of the three MDT groups. The ADR case reports (see Appendix 1 for a sample ADR case) contained anonymised demographic data for the patient, details of suspected drug(s) thought to be implicated in the ADR and concurrent medication, brief past medical history, and a description of the adverse reaction, treatment and outcome. The ADR case reports covered a range of therapeutic scenarios. The experience of the reviewers ranged from 2 to 31 years post qualification. Previous experience with formal ADR assessment ranged from none to minimal. None of the reviewers had any previous experience of assessing the avoidability of ADRs.

This was an internal validation study in which the avoidability tool was applied either by individuals or by groups that employed an informal method to reach consensus. The 'gold standard' for each assessment was the avoidability status assigned by a panel of two to three ADRIC senior investigators. This 'gold standard' was used to test whether groups were better than individuals. The ultimate goal is to roll out the LAAT. In order to support that roll out, reasons for variability between the responses, between participants and for any differences between individual and group assessments were explored.

A mixed methods approach was taken. Quantitative analysis examined the extent to which individuals and groups agreed with the 'gold standard' (the avoidability outcome set by a panel of senior investigators) using percentage exact agreement (%EA) (figure 1). An ethnographic approach, including non-participant observations of consensus meetings and post-consensus meeting semi-structured qualitative interviews, explored decision making and reaching agreement in consensus group meetings outlined in chapter 4.

3.4.1 Participants

Participants (nurses, pharmacists and doctors with experience of prescribing, administering, or dispensing medicines for children) were recruited via Alder Hey Children's NHS Trust through direct invitation or invitation through relevant line managers. For recruitment of the doctors we used snowball sampling to identify study participants where one of the senior clinicians introduced the study to a number of colleagues (6) who were then contacted directly and provided with information about the study. For recruitment of the nurses we liaised with the Research Nurse Manager and obtained a list of all the research nurses in the trust and their email addresses who we then contacted directly. We aimed to recruit 19 participants in total a mixture of nurses, doctors and pharmacists from a variety of specialities with varying levels of experience. All eligible participants received a written study information leaflet electronically and a consent form to confirm agreement to participate in the study with a request to reply within three weeks of receipt of the study information. Non-respondents were contacted for a second time and invited to participate.

After experiencing a low response rate from pharmacists, I was invited to go and speak to a group of pharmacists in the pharmacy department to give a brief overview of the study, raise the study profile and explain what was involved in taking part. The search for doctors to take part was widened by contacting the paediatric trainees via email through Mersey Deanery and North West Deanery. Once reviewers agreed to take part they were assigned to either one of the three consensus groups (A/B/C) or to the individual assessment group (10 reviewers independently assessed the cases). This was based on clinician type and availability for meetings. Each consensus group was made up of a multidisciplinary team (nurse, pharmacist, doctor). Group consensus meetings were arranged with clinicians who agreed to take part and written consent was taken prior to the

meeting. Consensus meetings were scheduled using Doodle® polls to check availability with participants.

The inclusion criteria for the study were:

- Clinicians (nurse, pharmacist, doctor) all levels/grades working in paediatrics

The exclusion criteria for the study were:

- Members of the ADRIC study group, the rationale being that they may introduce bias or show the effects of “group learning”.

The impact of using ST6-ST7 doctors and research nurses and their ability to contribute or participate in the consensus meetings may mean the results of the validation are not generalisable (results from ST6-ST7 doctors may be generalisable to other ST6-ST7 doctors but possibly not to other groups of medical staff). The groups may not have been the “ideal” makeup for validating an avoidability assessment tool due to lack of experience of familiarity/training in ADRs. On the other hand Consultant staff were more difficult to engage and would not necessarily have specific experience with assessing ADRs. A practical approach was taken to the allocation of reviewers to the consensus groups. It is likely that the impact of this was reduced inter-rater reliability.

3.4.2 Individual assessments

Nine reviewers (a mixture of nurses, pharmacists and doctors) independently assessed the selected 20 ADR case reports in their own time. Details of the individual reviewers are outlined below in Table 3.2. They were asked to plot their responses/selected pathway on the tool choosing one of the four possible outcomes on the LAAT (see Figure 2.5, Chapter 2) (‘Not avoidable’, ‘Possibly avoidable’, ‘Definitely avoidable’, ‘Unassessable’).

Table 3.2 Details of the individual reviewers

Clinician type	Specialty	Grade or number of years' experience
Doctors		
D1	Renal	ST6 - ST7
D2	Rheumatology	ST6 - ST7
D3	Respiratory	ST6 - ST7
Nurses		
N1	PICU/Research	< 10 years paediatrics
N2	Research	>10 years paediatrics
N3	Research/surgical	>10 years paediatrics
Pharmacists		
P1	Specialist paediatric pharmacist	> 10 years qualified
P2	Specialist paediatric clinical pharmacist	< 10 years qualified
P3	Specialist paediatric pharmacist	< 10 years qualified

3.4.3 Consensus Meetings

At the start of each consensus meeting the groups were provided with a brief overview of how the meeting would proceed. They were given the opportunity to ask any questions about the process.

The selected ADR case reports (Table 3.1) were assessed (see appendix 2 for the LAAT glossary and a guide to completing assessments) by each group. Groups were given 3 hours to assess the 20 ADR case reports. If they were unable to reach a consensus decision they recorded 'no consensus reached' for the particular case report.

The group meeting was overseen by a facilitator who did not take part in the assessment process but moderated the meeting. The facilitator JD was a member of the ADRIC study team. The group consensus meetings were also observed. Nonparticipant observation of the meetings were performed by LB who acted as an

observer to monitor the group interactions and see how groups decisions were made, discussed in Chapter 4.

3.4.4 Data analysis and statistical considerations

The number of cases was limited in order to avoid asking the teams to meet on more than one occasion to complete assessments. More than one meeting was not feasible and could potentially contaminate the results. This was a sample of convenience taking account of the availability of potential participants and of the study team. The sample size ruled out the possibility of calculating kappa scores (as a minimum of 40 cases is required for this which was not feasible for this study). Percentage exact agreement (%EA) was calculated for comparison.

The extent to which individual and group assessments agree with the assessments made by the panel of senior ADRIC investigators. Main outcome measure: For each individual or group, the percentage exact agreement with the panel of senior investigators.

Analysis: The overall series agreement for individuals and groups was summarised using descriptive statistics, means with standard deviations alongside the exact agreement statistics.

3.4.5 Ethics approval

a) Clinical data. The study involved the use of existing data held in routine clinical records which was collected during the ADRIC programme. The ADRIC programme was conducted with Trust approval. The Chair of an LREC agreed that the extraction of the clinical data from routine records did not required ethics approval. Accordingly, the use of this anonymised dataset did not require approval from the integrated research application system (IRAS). Approval was sought from the

Research and Development (R&D) department at Alder Hey NHS Foundation Trust for the use of this data in this study.

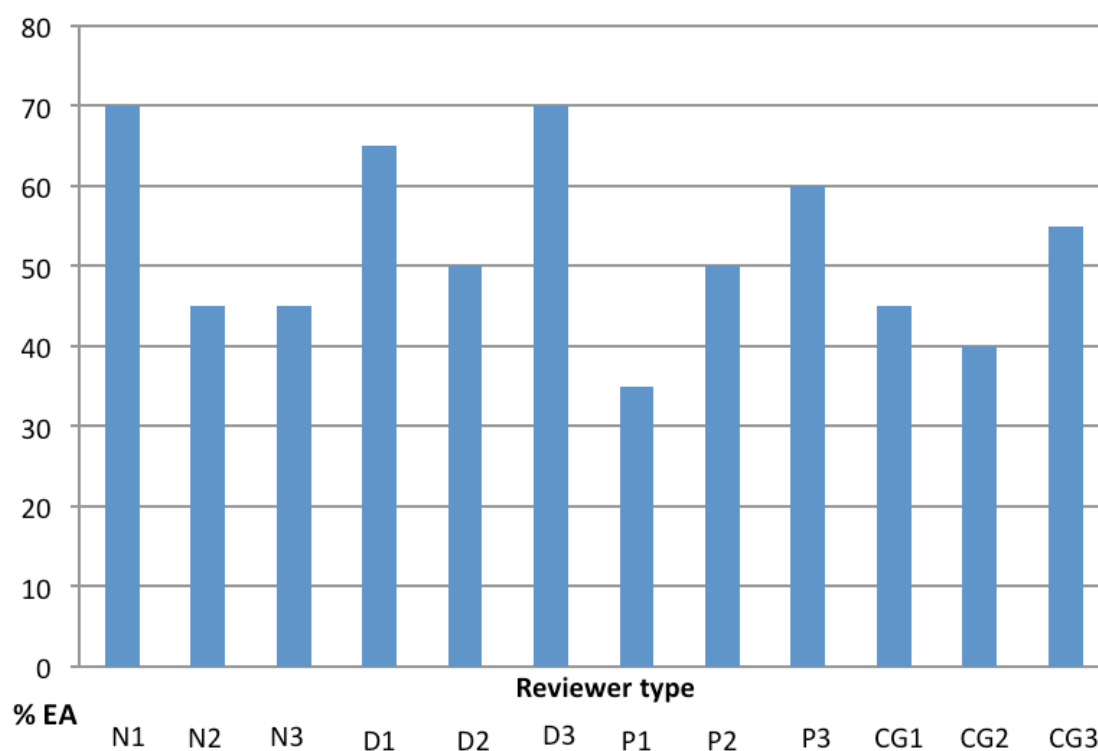
b) Participants. The participants in the study were all NHS employees who are recruited by virtue of their professional role and therefore this study did not need NHS REC approval. We sought management approval for the study from the R&D department at Alder Hey for employees to take part in the study. All participants consented to participate in the study and to take part in an interview where applicable (only those involved in the consensus groups). Sample participant information sheets and a consent form are shown in Appendix 3.

c) University of Liverpool (UoL). As this project was part of a PhD thesis. We gained approval from the University of Liverpool Committee for Research Ethics and we also obtained sponsorship from UoL (Sponsor Ref: UoL001004).

3.5 Results

Qualitative and quantitative analyses were carried out. We examined the extent to which individuals and groups agreed with the 'gold standard' using %EA (Figure 3.1). Agreement ranged from 35-70%. The mean agreement for individuals was 54% (SD 12.4) and 47% (SD 7.6) for the consensus groups.

Figure 3.1 Graph showing percentage exact agreement versus reviewer type



Key

Individuals:

N: Nurse 1,2,3

D: Doctor 1,2,3

P: Pharmacist 1,2,3

Groups:

CG: Consensus group 1,2,3

Table 3.3 shows the distribution of avoidability categories using the LAAT. The majority of assessments were 'not avoidable' for all reviewers. Overall the consensus groups were more likely to attribute a 'definitely' or 'possibly' avoidable assessment to the cases than the individuals.

Table 3.3 Distribution of avoidability categorisation using the LAAT

Clinician/Group	Definitely avoidable	Possibly avoidable	Not avoidable	Unassessable
Nurse 1	0	2	18	0
Nurse 2	4	4	11	1
Nurse 3	1	4	13	2
Doctor 1	6	1	12	1
Doctor 2	2	9	8	1
Doctor 3	5	4	10	0
Pharmacist 1	2	4	12	0
Pharmacist 2	2	4	14	0
Pharmacist 3	9	2	9	0
Consensus group 1	7	2	10	1
Consensus group 2	7	3	9	1
Consensus group 3	5	3	11	1
Gold standard	5	3	12	0

Table 3.4 shows the results from the individual reviewers and the consensus groups compared to the 'gold standard' (GS). It shows that some cases lead to complete agreement. Other cases lead to wide divergence. This includes some groups or individual assessors saying definitely avoidable and others saying unavoidable. There was also complete agreement and complete divergence between groups and individual assessors and the gold standard. The cases where disagreement occurred are denoted in red.

Table 3.4 Avoidability category assignments of individual reviewers and consensus groups - a comparison to the ‘gold standard’

ADRID	ADR Type	Gold standard	N1	N2	N3	D1	D2	D3	P1	P2	P3	Consensus group 1 (4/2)	Consensus group 2 (10/2)	Consensus group 3 (26/02)
1554	Vomiting	Definitely avoidable	Not avoidable	Not avoidable	Not avoidable	Definitely avoidable	Definitely avoidable	Definitely avoidable	Definitely avoidable (SPC)	Not avoidable (AH chemo N+V)	Not avoidable	Not avoidable	Not avoidable	Not avoidable
383	Procedural vomiting	Definitely avoidable	Not avoidable	Possibly avoidable	Possibly avoidable	Definitely avoidable	Definitely avoidable	Definitely avoidable	Not avoidable (AH PCA guideline)	Definitely avoidable (AH PONV)	Definitely avoidable	Definitely avoidable	Definitely avoidable	Definitely avoidable
138	Somnolence	Definitely avoidable	Not avoidable (BNFC)	Possibly avoidable	Not avoidable	Not avoidable	Possibly avoidable	Possibly avoidable	Not avoidable	Not avoidable	Definitely avoidable	Not avoidable	Not avoidable	Possibly avoidable
2103	Immunosuppressant drug level increased	Definitely avoidable	Not avoidable	Not avoidable	Possibly avoidable	Definitely avoidable	Possibly avoidable	Definitely avoidable	Possibly avoidable (SPC)	Possibly avoidable (BNFC)	Definitely avoidable	Definitely avoidable	Definitely avoidable	Definitely avoidable
1294	Constipation	Definitely avoidable	Not avoidable	Definitely avoidable	Not avoidable	Definitely avoidable	Possibly avoidable	Definitely avoidable	Not avoidable (AH PCA guideline)	Possibly avoidable (BNFC)	Definitely avoidable	Definitely avoidable	Definitely avoidable	Not avoidable
630	Hallucination	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Unassessable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Definitely avoidable	Unassessable
2105	Cardiac failure	Possibly avoidable	Possibly avoidable	Definitely avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable (SPC)	Not avoidable	Possibly avoidable	Not avoidable	Not avoidable	Not avoidable
293	Respiratory depression	Possibly avoidable	Possibly avoidable	Not avoidable	Possibly avoidable	Definitely avoidable	Possibly avoidable	Possibly avoidable	Possibly avoidable (AH PCA)	Not avoidable	Not avoidable	Definitely avoidable	Definitely avoidable	Possibly avoidable
2015	Flushing	Not avoidable	Not avoidable	Not avoidable	Unassessable	Not avoidable	Not avoidable	Not avoidable	Possibly avoidable	Not avoidable	Not avoidable	Possibly avoidable	Possibly avoidable	Not avoidable
252	Pruritus	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable (AH pain guideline)	Not avoidable	Not avoidable	Definitely avoidable	Definitely avoidable	Definitely avoidable
2258	Visual disturbance	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Unassessable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable
9	Diarrhoea + Excoriation	Not avoidable	Not avoidable	Possibly avoidable	Not avoidable	Not avoidable	Possibly avoidable (could have	Not avoidable	Possibly avoidable	Possibly avoidable	Possibly avoidable	Definitely avoidable	Definitely avoidable	Possibly avoidable

Table 3.4 Avoidability category assignments of individual reviewers and consensus groups - a comparison to the 'gold standard' (continued)

							used orobase paste following similar problem as neonate)							
1518	Hypocalcaemia + Hypophosphataemia	Not avoidable	Not avoidable	Unassessable	Possibly avoidable	Not avoidable	Possibly avoidable (could have checked Ca level after each infusion?)	Possibly avoidable	Not avoidable	Possibly avoidable	Definitely avoidable	Possibly avoidable	Not avoidable	Not avoidable
2815	Haematemesis	Not avoidable	Not avoidable	Possibly avoidable	Unassessable	Possibly avoidable	Possibly avoidable	Definitely avoidable	Possibly avoidable	Not avoidable	Not avoidable	Unassessable	Possibly avoidable	Not avoidable
477	Hypertension	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Possibly avoidable	Not avoidable	Not avoidable	Definitely avoidable	Possibly avoidable	Definitely avoidable
2844	Infusion associated reaction	Not avoidable	Not avoidable (BNFC)	Not avoidable	Definitely avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Definitely avoidable	Not avoidable	Not avoidable	Not avoidable
1224	Urinary retention	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Possibly avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable
1263	Clostridium difficile colitis	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Possibly avoidable (previous episode of C. diff)	Possibly avoidable	Not avoidable	Definitely avoidable	Definitely avoidable	Not avoidable	Unassessable	Not avoidable
493	Stomatitis	Not avoidable	Not avoidable	Definitely avoidable	Not avoidable	Definitely avoidable	Possibly avoidable	Not avoidable	Possibly avoidable	Not avoidable	Definitely avoidable	Not avoidable	Not avoidable	Not avoidable
1572	Hypoglycaemia	Possibly avoidable	Not avoidable	Definitely avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Not avoidable	Definitely avoidable	Not avoidable	Not avoidable	Definitely avoidable
	% Agreement	70%	70%	45%	45%	65%	50%	70%	35%	50%	60%	45%	40%	55%
	Guideline consulted	2 x BNFC	Web MD	BNFC				0		4 (2 x BNFC, 2 x AH)				
	% Avoidable	40%	10%	42% ³	28% ³	37% ³	55%	45%	45%	30%	55%	45%	50%	42% ³

³ For some reviewers % avoidability is out of 18 or 19 not 20 due to unassessable cases

3.5.1 Examples of cases with complete agreement or divergence

ADRID 1554 – Vomiting

The GS assessment was 'definitely avoidable' and overall agreement for this was 4/12. Among individual reviewers, 4/9 agreed with the 'gold standard'. There appeared to be a pattern related to profession with all three of the doctors and one pharmacist categorising the case as definitely avoidable. The other two pharmacists and all three nurses deemed the case not avoidable. In contrast all three consensus groups thought the case was not avoidable.

ADRID 383 – Procedural vomiting

The GS assessment was 'definitely avoidable'. Overall agreement for this case was 8/12. There was complete agreement between the consensus groups and the GS. In terms of the individual assessors 5/9 agreed with the GS. Of the remaining four reviewers, two categorised the ADR as possibly avoidable and two reviewers assessed the ADR as not avoidable. All three consensus groups agreed with the 'gold standard' and categorised the ADR as definitely avoidable.

ADRID 252- Pruritus

The GS assessment was 'not avoidable'. All the individual assessors (9/9) agreed with the GS. In contrast, all three consensus groups categorised the ADR as definitely avoidable.

ADRID 1572- Hypoglycaemia

The GS assessment was 'possibly avoidable'. There was complete divergence between groups and individual assessors and the gold standard for this case. Overall, 9/12 assessments categorised the case as not avoidable and the remaining three as definitely avoidable. Seven individual assessors categorised the ADR as not avoidable and the remaining two categorised the ADR as definitely avoidable. Two of the three consensus groups categorised the ADR as not avoidable and the third group categorised the ADR as definitely avoidable. Again there was a pattern seen in terms of professions with all three doctors in agreement and categorising the ADR as not avoidable.

ADRID 630 - Hallucination

There was almost complete agreement with the GS for this case with 9/12 assessments categorising the ADR as not avoidable. Eight out of nine individual reviewers categorised the ADR as not avoidable and the ninth individual reviewer categorised the ADR as unassessable. Of the three consensus groups one group assessed the case as not avoidable, one consensus group CG2, categorised the ADR as definitely avoidable and the third consensus group deemed the ADR unassessable.

ADRID 2815- Haematemesis

Overall there was poor agreement with the GS for this case (4/12). There was divergence between individual assessors and the groups. In terms of the individual assessors 3/9 agreed with the gold standard, 4/9 categorised the ADR as possibly avoidable, one individual categorised the ADR as definitely avoidable and one individual deemed the ADR unassessable. Two of the three individual pharmacists were in agreement with the GS. All three doctors categorised the ADR as avoidable either possibly or definitely. Of the three consensus groups, one group agreed with the gold standard, one group categorised the ADR as possibly avoidable and one group deemed the ADR unassessable.

ADRID 493- Stomatitis

The GS for this case was not avoidable. There was complete agreement with the GS from the consensus groups. The individuals had mixed agreement with the GS. 4/9 individuals agreed with the gold standard, 3/9 individuals categorised the ADR as definitely avoidable and the remaining two individuals categorised the ADR as possibly avoidable.

Cases with poor agreement included the diarrhoea and excoriation case. It was categorised as 'not avoidable' by the 'gold standard' group with only 3/9 individuals agreeing with the 'gold standard', the remaining six individuals and the three consensus groups all classified the ADR as either 'possibly' or 'definitely' avoidable. It was noted at the time of assessment in the 'gold standard' consensus group that

this case had a learning point attached to it. The case involved two separate ADRs the effect of the antibiotic and then the effect of the diarrhoea. The Senior Investigators noted that if they were being presented as separate ADRs they might have classified the excoriation as 'possibly avoidable' but on balance the ADR was classified as 'not avoidable'. They felt that if you've got two interactions one may be dependent on the other.

3.5.2 Likert scale feedback

The participants were asked to complete Likert scale feedback forms once they had completed their assessments. Table 3.5 shows the Likert scale summary results for the consensus groups (see Appendix 4 for details of feedback surveys and Appendix 5 for the full results from the Likert scales). The majority of reviewers thought the tool was easy to use. However, there was strong agreement that some questions on the LAAT were harder to answer and almost all reviewers agreed that in some cases it was difficult to know whether guidelines were available. Overall the reviewers were undecided if they would have been able to answer the questions by themselves, three reviewers (one pharmacist, one nurse and one doctor) felt they would be unable to answer all the questions by themselves. Two reviewers a pharmacist and a doctor agreed that they could have answered all the questions by themselves. Almost all reviewers thought the tool could be useful in the future.

Table 3.5 Likert scale summary results for consensus groups

	Strongly Agree	Agree	Undecided	Disagree	Strongly Disagree
The LAAT was easy to use		7	2		
I found some questions harder to answer (for some questions it was difficult to decide between a positive and negative response)	3	6			
In some cases it was difficult to judge whether guidelines or information were available	1	7		1	
I would have been able to answer all the questions by myself		2	4	3	
The tool could potentially have some utility in the future	4	4	1		

Additional comments from reviewers:

"Sometimes difficult to assess if a 'management plan' was adhered to!"

"Perhaps the tool would have future potential value with modification to include consideration of ADR and deliberate decision to proceed in a certain course of action"

"Useful tool"

"Was appropriate action taken box- should include addendum to detail that side effect/ADR was considered but that benefit to patient outweighed risk. Were there known preventative strategies box should include footnote to list considerable guidance e.g. protocols/NICE/Journal"

Table 3.6 Likert scale summary results for individual assessments

	Strongly Agree	Agree	Undecided	Disagree	Strongly Disagree
The LAAT was easy to use.	2	5	1	1	
I found some questions harder to answer (for some questions it was difficult to decide between a positive and negative response)	2	6		1	
In some cases it was difficult to judge whether guidelines or information were available	2	5	1	1	
It may have been easier to assess the cases in a group setting	3	1	3	2	
The tool could potentially have some utility in the future	5	3	1		

Additional comments from reviewers:

"Not always easy to judge if other sources of info are available."

"I had to use BNFC, nurses' dictionary and google for clarification of drugs and conditions"

Table 3.6 shows the Likert scale summary results for the individuals. Overall the individual reviewers agreed that the LAAT was easy to use with one reviewer, a doctor disagreeing and a second reviewer, a pharmacist undecided. Similar to the consensus group results the majority of individual reviewers felt that some questions were harder to answer with one reviewer, a pharmacist disagreeing. In terms of thoughts on assessing the cases as a group or individually three reviewers strongly agreed that it may be easier in a group setting (two nurses and one pharmacist). Two individuals (a pharmacist and a doctor) disagreed that it might be easier in a group setting and the others were undecided. Overall nearly all of the reviewers felt the tool could be useful in the future.

3.6 Discussion

Assessing the avoidability of ADRs is a complex process that requires taking into account a number of variables. The literature has shown that avoidability assessments are challenging. A variety of tools are available, ranging from the implicit to explicit. None of the available tools has been widely accepted (Hakkarainen et al. 2012a). There is currently no standardised method for determining ADR avoidability and many of the established tools are not suitable for use in paediatric practice. A systematic review found that several definitions exist for avoidability as a consequence of the variability in methodological approaches to assessment of avoidability, and none fits all circumstances (Ferner, Aronson 2010b).

A recent systematic review on ADRs in children noted the absence of avoidability data; this highlighted the need for work in this area. We followed the recommendations outlined by Hakkarainen et al. (2012) They recommended that future studies include reliability and validity testing; take action to standardise the measurement process; provide information on the assessors in terms of training and experience in assessing preventability; and describe how the assessments took place (i.e. whether cases were assessed independently or via consensus and how any disagreement is dealt with) (Hakkarainen et al. 2012a).

Following our initial testing of the LAAT with individuals it was decided to investigate if group avoidability assessments were superior to individual avoidability assessments. It was hypothesised that MDT groups would be superior to individual assessments given the nature of the assessments. However, agreement with the 'gold standard' was similar for individuals and groups. In terms of %EA individuals had marginally better agreement with the 'gold standard' than the consensus groups. Given the logistic difficulties with groups, individual assessments can be used in further work. Feedback from individuals was generally positive with most participants agreeing that the tool was easy to use and that it might have potential utility in the future. Differences were observed between the three professions with doctors on average having the best agreement with the 'gold standard'. The perceived good agreement between nurse (N1) and the 'gold standard' at 70% may have been falsely elevated as when you look at the distribution of avoidability categories, N1 classified 18/20 ADRs as 'not avoidable'. This was significantly higher than the other individuals and consensus groups and may have falsely magnified agreement with the 'gold standard'.

On reflection, the reviewers who took part in the consensus groups may not have been the "ideal" group members. As in order to assess avoidability there is a requirement to have an understanding of what an ADR as it becomes difficult to assess avoidability if the reviewer does not believe an ADR has occurred in the first place. Ideally, reviewers with some understanding of pharmacovigilance would be preferable and perhaps more senior clinicians would be more naturally placed to assess avoidability. For example, members of the Drug and Therapeutic Committee, staff from the Yellow Card centres or more experienced nurses, pharmacists and consultant level doctors may have been a more appropriate choice. This group might have shown improved inter-rater reliability. This could be investigated in future work; to look at the impact of having more experienced group members assess avoidability and compare inter-rater reliability between the different groups.

External validity testing using expert groups would overcome the lack of understanding about ADRs and confusion over terminology and is therefore likely to improve the tool's IRR.

In terms of the reviewers used in this study; on one hand Nurse Prescribers may have been a better choice for example if ADR cases were grouped by speciality and the aim was to have expert reviewers assessing the cases. However, if the ADR cases were more variable in nature as was the case in the consensus and individual testing phases (Chapter 3 and 4) then the use of Nurse Practitioners who are highly specialised with an in-depth knowledge of a particular area for example oncology or respiratory might be beneficial in some instances but possibly also have a downside. The downside of using Nurse Practitioners may be the loss of the perspective of the nurse into what happens at the ward level and in some ways this might result in the loss of the MDT effect. In terms of Junior Doctors conducting assessments the tool highlighted the need for further training in the area of ADRs and pharmacovigilance. Whilst it may have been more appropriate and indeed also resulted in improved IRR to use more senior doctors, the groups and individuals were made up of people who had volunteered to take part in the assessments. In terms of validation of the methodology the clinicians chosen may not have been the right group but in terms of application they may have been as this was a balance between expert validation of a tool and testing in a real-life practical setting.

The consensus groups were more inclined to attribute a 'definitely' or 'possibly' avoidable assessment to the cases than the individuals. The consensus groups also consulted more guidelines than the individuals (or at least those individuals that specified if guidelines were consulted) this may have been because a laptop computer was made available to the groups. Other reasons for this including differences between professions will be discussed in the qualitative analysis in Chapter 4.

The cases were informative with marked divergences for some ADR types. Possible reasons for divergence might be evidence based, practice based or irreducible divergence. The small sample size means caution should be taken with over interpretation of the data but the divergences show what is possible for avoidability assessment within the parameters of this assessment. The cases denoted in red in Table 3.4 show some examples of divergences. There may be limits to the extent of agreement about avoidability that can be reached between individuals or groups. The LAAT appears to support consistent assessments by a single assessor or within a group. Given that 16/18 of assessors agreed, or strongly agreed that the LAAT was potentially useful in future, the LAAT has face validity for paediatrics. Thus LAAT is likely to provide an improvement on global introspection or unstructured reflection on a case. However, the process we describe involving the LAAT was not sufficient for consistency between assessors or between groups. Consistency between assessors and groups would require similar attitudes to accessing and interpreting guidelines. Furthermore, as discussed in Chapters 5 and 6, similar and additional differences to the assessment of avoidability were found between individuals (see divergent cases in Chapter 5). A preliminary finding, which will be developed in later chapters, is that consistent assessment of the avoidability of ADRs appears to need more than the provision of an assessment tool. In the Likert feedback results some individuals agreed that it may have been easier to assess the cases in a group setting however some were undecided and two disagreed. The feedback from the groups showed that most were undecided whether they would have been able to answer the questions themselves. Given that the individual assessors had not been exposed to the group assessments this could indicate that assessors would tend towards preferring a group process if that assessor had experienced both models. Alternative study designs are discussed in section 6.3 in Chapter 6.

3.7 Conclusion

In assessing the avoidability of ADRs individual assessments had better agreement with a 'gold standard' evaluation than group assessments. Overall, the LAAT showed face validity for use in paediatrics. It showed that some cases lead to complete agreement. Other cases lead to wide divergence. There was also complete agreement and complete divergence between groups and individual assessors and the gold standard. Given the logistic difficulties with groups, individual assessments can be used in further work. Qualitative analysis of observations and participant interviews may help identify reasons for this and inform the optimisation of a tool for assessment of ADR avoidability. Chapter 4 examines the qualitative aspects of the study.

Chapter 4: Qualitative Work- group processes and decision making in MDT consensus meetings

4.1 Introduction

There has been an increased use of qualitative methods in healthcare research in recent years (Britten 2005). As defined by Hakim (1997), qualitative research provides the:

Individuals' own accounts of their attitudes, motivations and behaviour. It offers richly descriptive reports of individuals' perceptions, attitudes, beliefs, views and feelings, the meanings and interpretations given to events and things, as well as their behaviour; displays how these are put together, more or less coherently and consciously, into frameworks which make sense of their experiences...(Hakim 1997:26).

Qualitative research can provide rich descriptions which cannot be generated through quantitative methods (Pope, Mays 1995) and can, therefore generate rich and detailed accounts of clinicians' professional and inter-professional relationships (Reeves, Kuper & Hodges 2008) especially in exploring the complexities of clinical decision making; a phenomenon that cannot be explored using purely quantitative methods (Pope, Mays 1995). For example, Kidger et al (2009) used a qualitative approach to explore the factors that influence the clinical decision making in a MDT gynaecological cancer team. They used non-participant observations and semi-structured interviews. It emerged from their observations that decision making tended to take one of three paths: discussion quick and decision clear, discussion long, ends with agreement and clear decision and finally, discussion long, no clear decision and unresolved questions (Kidger et al. 2009).

The increased use and awareness of the contribution of qualitative research methods within healthcare research has led to scrutiny of qualitative research

(Murphy et al. 1998b). There has been considerable debate over whether qualitative and quantitative methods can be assessed according to the same quality criteria (Hannes K et al. 2011). However, such debates often fail to engage with the goals of qualitative research methods which are designed to construct an understanding rather than provide statistically significant generalisable findings. As Devine (2002) has argued, qualitative research is appropriate where “the goal of a piece of research is to explore people’s experiences, practices, values and attitudes in depth and to establish their meaning for those concerned” (Devine 2002:207).

The aim of this research was to generate an understanding of how clinicians make decisions individually and within a MDT context and how those decisions lead to quantifiable outcomes. As such, both qualitative and quantitative approaches were taken here. This chapter provides a description and justification of the methodological approach taken in this research. It will firstly examine the different research paradigms. It will go on to explain the rationale for choosing a mixed methods approach and describe the approach taken here. It will also describe the method of analysis employed in this study. This will offer some personal reflection of the research process. Then the results will be presented and finally the discussion.

Research paradigms

A paradigm is a belief system or theory that guides the way we do things, or more formally establishes a set of practices. This can range from thought patterns to action. According to Guba (1990), paradigms can be characterised through their: ontology (what is reality?), epistemology (how do you know something?) and methodology (how do we go about finding out?) (Guba 1990). These characteristics create a holistic view of how we view knowledge: how we see ourselves in relation to this knowledge and the methodological strategies we use to discover it. Denzin and Lincoln (2003) described research paradigms as a ‘net’ that contains the researcher’s ontological and epistemological approaches. It is the choice of paradigm that sets down the intent, motivation and expectations for research (Mackenzie, N. & Knipe, S. 2006). The theoretical framework or paradigm influences

the way knowledge is studied and interpreted. In the absence of a paradigm from the start, there is no basis for subsequent choices regarding methodology or research design (Mackenzie, N. & Knipe, S. 2006) and it is difficult to assure the quality of the research.

Guba and Lincoln (1994) break down research paradigms into three aspects. First of all many paradigms have an ontology, an assumption about the nature of reality. Secondly, each paradigm has an epistemology, a set assumptions about the relationship between the "knower" and the "known." A particular researcher's take on knowing is known as their epistemological stance. Finally each paradigm contains some assumptions about methods, though none are restricted to simply one way of gathering and analysing data. Table 4.1 outlines the different research paradigms.

Table 4.1 Research paradigms adapted from (Guba, E.G. and Lincoln, Y.S. 1994, Creswell 2009, Mackenzie, N. & Kipe, S. 2006)

Paradigm	Ontology	Epistemology	Methodology (?)
Positivism	Realism. There is a "real," objective reality that is knowable	Objectivist. The researcher can, and should, avoid any bias or influence on the outcome. Results, if done well, are true.	Verification of hypothesis. Tends toward quantification and controlled experiments.
Post-positivism	Critical Realism. There is a "real," objective reality, but humans cannot know it for sure.	Modified Objectivist. The goal is objectivity, but pure objectivity is impossible. Results are "probably" true.	Includes both qualitative and quantitative methods. Modified experimental/manipulated. Seeks reduction of bias through qualitative validity techniques (e.g. triangulation)
Critical Theory	Historical Realism. Reality can be understood, but only as constructed historically and connected to power.	Knowledge is mediated reflectively through the perspective of the researcher.	Focused on investigator/participant dialogue. Dialogic.
Constructivism	Relativist- local and specific constructed realities. All truth is "constructed" by humans and situated within a historical moment and social context. Multiple meanings exist of perhaps the same data.	Researcher and participants are linked, constructing knowledge together. Transactional/subjectivist findings.	Generally qualitative, research through dialogue.
Pragmatism	Varied. Pragmatists may be less interested in what "truth" is and more interested in "what works"	Accepts many different viewpoints and works to reconcile those perspectives through pluralistic means	Focuses on a real world problem, by whatever methods are most appropriate, and tends toward changes in practice. Qualitative and /or quantitative methods may be employed.

Ontology is what one believes exists and is a view on the nature of reality. Are you a realist or, a relativist? Ontological assumptions are concerned with what constitutes reality, in other words what is. Epistemology is our perceived relationship with the knowledge we are uncovering. Are we part of constructing that knowledge or does knowledge exist independently and external to us? It is concerned with how knowledge can be created, acquired and communicated or what it means to know. Guba and Lincon (1994, p. 108) explain that epistemology asks the question, what is the nature of the relationship between the would-be knower and what can be known? The researcher's viewpoint will frame their interaction with what they are researching and is dependent on their ontological view. This in turn affects the methodology and the approach to gathering knowledge and conducting the research. According to Wainwright (1997) methodology is your strategic approach, rather than your techniques and analysis. Together the three (ontology, epistemology and methodology) constitute the philosophy of a paradigm.

Positivist paradigm

Positivist approaches are based on an ontology that the things we experience are things that exist. Studies are based on facts and consider the world to be external and objective. A deductive approach begins with theories that are tested against new data with an emphasis on the replication and generalisability of findings. Deduction is defined by Babbie (2013) as *"the logical model in which specific expectations of hypotheses are developed on the basis of general principles"* (Babbie 2013). A deductive approach is informally known as the "top-down" approach as the reasoning works from general to more specific, narrowing down into specific hypotheses that can be tested thereby confirming or rejecting our original theories. It is often referred to as 'scientific research'. Positivist research is typically aligned with quantitative methods (Mackenzie, N. & Knipe, S. 2006). According to Coffey (1999) strict scientific research requires the researcher to be objective but in 'real life' a researcher does not find out things by remaining distant. It is impossible to remove the influence of the researcher (Coffey 1999).

Interpretivist/constructivist paradigm

Each individual constructs his/her own reality so there are multiple interpretations. It tends to rely on the *"participants views of the situation being studied"* (Creswell 2003). Constructivists do not usually begin with a theory they develop, refine, amend or support theory throughout the research process (Mackenzie, N. & Knipe, S. 2006). An inductive approach begins with specific data out of which more general ideas or theories are generated. An inductive approach is also called the "bottom up" approach as the reasoning begins with specific observations and moves towards broader generalisations. Inductive reasoning, by its very nature, is more open ended whilst deductive reasoning is narrower and is concerned with testing or confirming hypotheses (Trochim 2006).

According to Strauss and Corbin (1998) the concept of induction is often applied to qualitative research and although hypotheses may evolve from data there is interpretation of data to some extent which they class as a form of deduction. They acknowledge that there is a human element in analysis and there is overlap between induction and deduction (Strauss, Corbin 1998).

Rationale for mixed methods approach

Traditionally research was thought of as being either quantitative or qualitative however, over the past forty to fifty years mixed methods have increasingly been adopted into practice (Creswell 2003). According to Creswell 2003 p.4 *"the situation today is less quantitative versus qualitative and more how research practices lie somewhere on a continuum between the two"*. Mixed methods research is increasingly being conducted where the researcher combines quantitative and qualitative aspects (Anderson 2010).

According to Creswell (2003) there are three key questions which are fundamental to the design of research:

1. *What knowledge claims are being made by the researcher (including a theoretical perspective)?*
2. *What strategies of inquiry will inform the procedures?*
3. *What methods of data collection and analysis will be used?*

The research question and the aim of the study dictate the type(s) of method chosen. It is vital that the method or methods chosen relate directly to the research question and the aims of the study. Creswell (2003) therefore suggests consideration of these three elements in the design of a research study enables the researcher to identify whether a quantitative, qualitative or mixed methods approach is needed. In this study a mixed methods approach was taken as adopting a solely quantitative approach would not have answered the research question.

This chapter is about the behaviour of groups when using the LAAT. Our motivation for this research was the need to optimise group performance when using the LAAT and the need to optimise the LAAT (setup, explanation and use). In particular we were interested in levels of agreement between groups and extent of similarity in pathway taken when the LAAT was used. We were interested in the different approaches used by the consensus groups to assess the avoidability of the ADR case reports. Although we provided written instructions and a glossary relating to the use of the LAAT which contained information regarding the questions and their interpretation and provided practical examples the groups often chose not to consult the glossary even when they experienced problems with certain cases.

Quantitative analysis examined the extent to which individuals and groups agreed with the 'gold standard' as outlined in Chapter 3. The qualitative approach was adopted in addition to quantitative methods as one of the aims of the research was to explore the factors that influenced decision making in MDTs this could not have been done using quantitative methods alone. From this perspective qualitative methods were also used to gain an insight into clinician's thoughts, experiences and practices in relation to assessing the avoidability of ADRs.

Some researchers believe that mixed methods research should be linked to one paradigm only and pragmatism has been suggested as the research paradigm of mixed methods (Johnson, Onwuegbuzie 2004). More recently it has been suggested that multiple paradigms relate to different phases of research design, thus linking

paradigms to research design (Creswell 2011). The central premise of mixed methods research is that the combination of both qualitative and quantitative approaches provides a better understanding of the research question than either method would alone (Creswell 2011). This study began with a quantitative phase which reflected an initial postpositivist paradigm (Chapter 3) and then moved on to a qualitative phase described here in Chapter 4 where the stance taken was interpretive and reflects the constructivist paradigm. So, the selected ontological framework was a mixture of constructivism and critical realism. The selected epistemological framework could be described as both transactional and modified objectivist. The selected methodological framework was quantitative and qualitative including participant observation, semi structured interviews. With respect to Table 4.1 the research paradigms were post-positivism and constructivism.

Analysis was inductive and a thematic approach was taken in order to identify key themes that emerged from the data. According to Boyatzis (1998) thematic analysis is a process of "encoding qualitative information" (p. vii) where the researcher develops codes; words or phrases that serve as labels for sections of data (Boyatzis 1998). Thematic analysis is a systematic approach to the analysis of qualitative data that involves identifying themes then classifying data, according to themes, and interpreting the resulting thematic structures by seeking commonalities, relationships, patterns, theoretical constructs, or explanatory principles (Mills, Durepos, G & Wiebe, E 2010). Thematic analysis is used by researchers as a way of getting close to their data and developing deeper appreciation of the content. Often it is used as a first step prior to conducting further analysis and aims to identify key themes rather than generate theory. The use of grounded theory was considered as a way of analysing the data further and generating theory but insufficient data, time and resources available to conduct grounded theory therefore thematic analysis was chosen.

4.2 Aims

The study was designed to assess whether using the LAAT gave consistent results in the assessment of ADR cases. This part of the study aimed:

1. To explore the factors that influence decision making in a MDT consensus meeting.
2. To review group processes, such as turn taking, during a MDT consensus meeting
3. To review use of guidelines during a MDT consensus meeting

4.3 Ethical considerations

4.3.1 Ethics approval

As outlined previously in Section 3.4.4 in Chapter 3

4.3.2 Consent

All participants were given an information sheet to read. They had the opportunity to ask any questions before providing written informed consent see appendix 3 for the information sheet.

4.4 Methods

As described in Chapter 3, reviewers were either assigned to independently assess a selection of ADR cases reports or to one of the three MDT consensus groups. Participants were then notified as to which group they had been assigned to.

4.4.1 Sample size and selection of cases

ADR cases

The ADR cases were selected as outlined in Chapter 3, Section 3.3.3.

Definition of gold standard for each ADR

As outlined in Chapter 3, Section 3.3.3

Sampling

We used purposive and snowball sampling (non-probability sampling methods) to recruit participants as we wanted to explore a specific group of healthcare professionals. Purposive sampling is where members of a sample are chosen with a 'purpose' to represent a location or type in relation to a key criterion (Ritchie, J: Lewis, J (eds) 2003). Decisions about which criteria are used for selection are often made in the early design stages of the research and are informed by a range of factors including the principal aims of the study, existing knowledge about the area of work and hypotheses that the research may want to explore (Ritchie, J: Lewis, J (eds) 2003). The main decision regarding criteria for selection in this study was based on profession as we required a mixture of nurses pharmacists and doctors with experience of prescribing, administering, or dispensing medicines for children in order to facilitate MDT consensus groups.

Individual assessments

As outlined in Chapter 3, section 3.4.1

Consensus groups

Three MDT (nurse, pharmacist, doctor) consensus meetings were held. The group meetings were overseen by an independent facilitator (JD), a research pharmacist known to the team with experience in ADRs. JD was not involved in this study. JD moderated the meetings but did not take part in the assessment process and was not involved in the study analysis meetings. Prior to the meeting (48 hours before) reminder emails were sent to all participants; a copy of the avoidability tool glossary and a study information sheet were attached. On the day of the consensus meeting, JD provided a very brief overview of the ADRIC study programme to the group, explained the format of the session and introduced the LAAT.

The consensus groups were given 3 hours to assess the 20 selected ADR case reports from the ADRIC inpatient study. They were asked to map their responses and selected pathways on a copy of the tool for each case report selecting one of the four possible outcomes on the LAAT for each case ('Not avoidable', 'Possibly avoidable', 'Definitely avoidable', 'Unassessable') or if unable to reach a decision, to record an outcome of 'unsure'.

Description of the MDT consensus meetings

Meetings lasted up to 2.5 hours and took place in a dedicated meeting room at a paediatric medical and surgical secondary and tertiary referral centre in the Northwest of England (Alder Hey Children's Foundation Trust) with members seated around a table. The mean meeting time was 2 hours and 21 minutes and the range was 2 hours and 7 minutes to 2 hours and 39 minutes. A description of the consensus group meetings is outlined below in Table 4.2.

Table 4.2 Description of the consensus group meetings

Consensus Group	Meeting Date	Meeting Duration
Consensus group 1	04/02/2014	2.07.00
Consensus group 2	10/02/2014	2.17.58
Consensus group 3	26/02/2014	2.39.12

Nonparticipant observations of meetings

Nonparticipant observations of the consensus meetings were conducted by LB. Observations were recorded by hand during the meetings and the notes were typed up immediately afterwards.

Interviews

Semi structured interviews with team members were conducted over a four week period in February 2014 (4th-27th February) by LB. The consensus meetings took place on the 4th, 10th and 26th February. The post meeting interviews were conducted either immediately after the meeting or the following day for all

participants who took part. Before the study started potential participants were contacted by LB to inform them of the study and gain initial consent to be contacted again. Informed written consent was gained from each participant prior to the consensus meeting and interview. The nine reviewers involved in the consensus meetings were invited to take part in semi-structured interviews after the consensus meetings. The purpose of the interviews was to explore reviewers' accounts of the consensus meetings, in particular their perceptions and views of the decision making process and their role in this and how future meetings could be improved. Topic guides were used to steer the interviews. The topic guide was developed by LB and reviewed and commented on by (JA and MT) (see appendix 6 for a copy of the topic guide). The interview topic guide was piloted with two other interviewees prior to the study to ensure questions and follow-up prompts were appropriate and feasible. Some changes were made as a result of this including the addition of extra prompt questions and clarification of some questions.

4.5 Recruitment of participants

The recruitment of participants was outlined in Chapter 3 section 3.4.1

4.6 The research process: personal reflections

At the beginning of the recruitment stage I was aware that it might be challenging to recruit enough participants and that arranging MDT consensus meetings may be difficult. I soon learned that even with detailed planning and scheduling that last minute changes were sometimes necessary due to clinical commitments. The first consensus meeting ended up being rescheduled after sickness resulted in staffing issues. The second meeting went ahead as scheduled and the third one was almost cancelled but went ahead after a last minute swap of doctors. This exemplified the extent of social networks as after sending an email request we had several volunteers who were aware of the study. We were able to go ahead with the third meeting as a doctor volunteered to attend at short notice to replace a colleague.

The role of reflexivity during data collection and analysis was also considered. Reflexivity addresses our subjectivity as researchers related to people and events that we encounter in the field. The process of reflexivity refers to the influence of the researcher's own position, views, and responses, which may be conveyed to participants, and which in turn, may result in participants continually adjusting their responses as the interview continues (Corbin, J. & Strauss, A. 2008). With this in mind I've reflected on my position as a researcher.

4.7 Reflections on interviewing and consensus groups

Interviewing was a new experience for me and whilst I had completed a two day introductory course on qualitative interviewing I was a bit apprehensive at first about conducting interviews myself. Being a pharmacist I guess somewhat helped prepare for this process as in clinical practice I would have gained some informal experience, practiced my listening skills and interpreted information provided. However, there were some differences between research and clinical practice for example; interviews conducted in the research setting were based on a topic guide whereas interviews in a clinical setting would not be based on a topic guide. Also in the case of this study, the interviews were conducted with other clinicians where typically in practice they are more likely to be with patients rather than clinicians and are probably conducted in a less structured and formal way. The first two interviews were conducted immediately after the first consensus meeting and they went well which gave me some confidence. Overall my topic guide worked well. I noticed how different interviewees responded to questions and how some provided more detail than others whilst some required additional prompting. Some interviewees needed further questioning with open questions in order to get the information I required.

I wondered if my position as a pharmacist would impact on interviewing other clinicians. The majority of the interviewees I had not met before or only knew by sight but one of the pharmacists I had met on a number of occasions previously and the other pharmacist I knew reasonably well as we had trained together. I

wondered before the interviews if it might be strange interviewing people I already knew but it turned out to be okay. I was aware that I might bring assumptions to the interviews however, the prompt guide helped offset any assumptions and ultimately, I don't think this made any difference to the results. Before interviewing the pharmacist who I knew particularly well I wondered if it might be a little bit awkward but if anything it seemed to be a good thing as there was already a rapport built up.

In terms of the consensus groups, I found being a non-participant observer challenging at times as despite the facilitator making my role clear when they provided the overview people still asked me questions on occasion. As a pharmacist I would normally be actively involved in discussion about medicines but on this occasion I could only observe not intervene. I found the second consensus meeting especially challenging when there were some issues at the beginning with interpreting the questions on the LAAT. I found it challenging at times not to comment or try and explain instead leaving the facilitator to explain. This was related to ownership of the study and I think also due to the implications of participants' misunderstanding the interpretation of the questions on the tool and the impact this would have on the study. As I was acutely aware that if this was not clarified there would have been problems throughout the assessments with the application of the LAAT.

4.8 Analysis

An exploratory approach was taken using thematic analysis. Thematic analysis was used to immerse oneself in the data, to organise and focus the data for interpretation. According to Marshall and Rossman (1999) thematic analysis can be divided into six phases:

1. Data organisation
2. Generation of categories or themes
3. Data coding
4. Testing emergent understandings of the data

5. Searching for alternative explanations of the data
6. Data analysis and write-up

Coding is the analytic strategy used in thematic analysis. Coding is a process which involves looking for recurrent themes or topics and highlighting similar sections of text with a 'code' to categorise them. The assigned codes are later used to support theoretical interpretation of the data.

The verbatim transcripts of the interviews and field notes recorded during the meetings were entered into NVivo 10 (qualitative data analysis software). The first step in thematic analysis is familiarisation with the data; this involved repeated reading of the transcripts followed by the generation of categories and emergent themes. The coding process initially involved line by line open codes which produced a large number of initial codes which were later refined into broader categories during analysis group meetings. JA, MT, JK, MPe and LB met to discuss emerging themes and develop analytical categories. Analysis was verified throughout by frequent review of transcripts to identify recurrent patterns and themes. LB led the analysis and development of the coding framework in a process that had both inductive and deductive aspects. She read transcripts several times to develop analytic categories regarding the content and meaning of particular transcript sections. LB also referred to the field notes during the analysis to prompt her recollection of contextual and process aspects of the interview and use these to help interpret the transcript sections. JA an experienced qualitative researcher was involved in the analysis as recommended by (Hannes K et al. 2011); experienced methodologists may have valuable insights into the analysis and can guide others through the critical appraisal process. JA, MT, MPe and JK supported the analysis by reading a sample of the transcripts and by 'testing' and developing the analysis through periodic discussion with LB. All five analysts compared within and between a sample of transcripts, and iterated between developing analytical categories and new data. Common themes were organised into a coding frame (see appendix 7 for coding framework). LB used the framework to analyse all subsequent transcripts. The coding frame was refined as the analysis progressed. Selected sections of

interview transcripts and observation notes were analysed by a second member of the study team. We used NVivo 10 to assist the analysis by indexing relevant sections of transcripts to facilitate interrogation of the data. We employed a number of methods that are recommended to help ensure rigour in the analysis of qualitative data. We examined the exceptional cases, that is, cases that were atypical either because of ADR type or clinicians' experiences and considered how differences between these and more typical cases could inform the analysis (Strauss, Corbin 1998, Lincoln, Guba 1985). The MDT investigator triangulation aimed to ensure the quality and clinical relevance of the analysis. The diversity of the analysis team gave a broad perspective as the team was made up of an experienced qualitative researcher, pharmacist, doctor and two other non-clinical researchers.

4.8.1 Analytical induction

This approach is an iterative process where data is analysed by reading and re-reading interview transcripts until themes emerge and concepts are developed. The concepts are refined until there is a clear fit with the data and the theory. Fielding provides a good description of the use of analytical induction in qualitative research:

Using analytical induction in qualitative research allows the researcher to identify some 'phenomenon' and generate a provisional hypothesis which is then examined further as a 'case'. A case is studied further to see whether the hypothesis relates to it. If not, the hypothesis is reformulated (or the phenomenon redefined to exclude the case). While a small number of cases support practical certainty, negative cases disprove the explanation, which is then reformulated. Examination of cases, redefinition of the phenomenon and reformulation of hypotheses is repeated until a universal relationship is shown (Fielding, 1988 cited in Silverman, 2011, p.374) (Silverman 2011).

Although analytical induction aims to develop concepts and theories from the data, in reality, no researcher is completely subjective but comes to the research process with preconceptions or 'theoretical lenses' based on experience and theoretical knowledge (Seale et al. 2006). In the research undertaken in this study there were some existing theoretical ideas or 'lenses' within which to view the data. These were drawn from existing work in the area which examined decision making in MDTs (Kidger et al. 2009, Lanceley et al. 2008). Kidger et al (2009) explored the factors that influenced decision making in MDTs and they identified three main themes central to the decision making process: the unsystematic consideration of patient related factors, the variation in team members' role and level of participation in discussions depending on their profession and finally, different pathways and outcomes of the discussions which took place. At the beginning of the study I already had some existing theoretical lenses particularly the effect of different professions on participation in the group, seniority effect and leadership skills. During the analysis group meetings we discussed the coded interviews and agreed on the following broad themes:

- Clinical Knowledge
- Conceptual awareness
- Perceptions of the tool
- Engagement with the tool
- Perceptions of groups v's individuals

4.8.2 Validity and reliability

The trustworthiness of qualitative research has been critiqued for being unrepresentative, subjective and lacking in reliability and generalisability. However, such criticisms often fail to appreciate the different aims of research and the appropriate methods necessary to achieve those aims. However, this does

not exclude the need for rigorous research and numerous frameworks for ensuring rigour in qualitative work have been proposed (Shenton 2004). Guba (1981) proposed four criteria to be considered by qualitative researchers in pursuit of a trustworthy study. The concepts outlined in table 4.3 are based on (Lincoln, Guba 1985) translation of criteria to critically appraise findings from qualitative research. We assessed credibility, transferability, dependability and confirmability the criteria outlined by (Hannes K et al. 2011, Lincoln, Guba 1985). Qualitative research has been criticised in the past as biased, anecdotal and lacking in rigour; however, when it is conducted properly it is reliable, credible, rigorous, valid and unbiased (Anderson 2010).

Table 4.3 Criteria to critically appraise findings from qualitative research (Hannes K et al. 2011)

Aspect	Qualitative Term	Quantitative Term
Truth value	Credibility	Internal Validity
Applicability	Transferability	External Validity or Generalisability
Consistency	Dependability	Reliability
Neutrality	Confirmability	Objectivity

Credibility

Lincoln and Guba (1985) argue that ensuring credibility is one of the most important factors in establishing trustworthiness. *“Credibility evaluates whether or not the representation of data fits the views of the participants studied, whether the findings hold true”* (Lincoln, Guba 1985). Evaluation techniques include: member checks, peer debriefing, negative case analysis, frequent debriefing, verbatim quotes and independent analysis of the data by more than one reviewer (Hannes K et al. 2011). This was achieved by the independent analysis of data by more than one researcher (LB, JA, MT, MP and JK) multiple researchers from different disciplines and they brought different views for example; MT focused on guidelines and contributed knowledge regarding existing guidelines whereas JA from a social

science background was interested in the distribution of power and turn taking during the consensus meetings. The different lenses which the researchers looked at the data through were interesting and contributed to the credibility of the data however; there was also considerable uniformity as the team had worked together before. Meetings were transcribed verbatim and distributed to all researchers for comments. Researchers met to discuss transcripts and this included interrogation of negative data and cases.

Transferability

“Transferability evaluates whether research findings are transferable to other specific settings.”

Evaluation techniques include providing details of the study participants, providing contextual background information and demographics (Hannes K et al. 2011). Lincoln and Guba (1985) suggested that it is the responsibility of the researcher to ensure sufficient contextual information is provided to enable the reader to make a transfer. We recognised that as this was conducted in a tertiary paediatric centre it was important to describe the context within which the study took place, participant characteristics and location have been described in the methods section. Transferability was assessed by providing the details of study participants, background information and demographics.

Dependability

“Dependability evaluates if the process of research is logical, traceable and clearly documented.”

Evaluation techniques include: peer review, triangulation, reflective appraisal of the project, research design and implementation and audit trails (Hannes K et al. 2011). Lincoln and Guba (1985) suggested that dependability is closely related to credibility. This was achieved by triangulation and reflexivity a self-critical account of the research process, weaknesses and problems overcome. The whole study was overseen by an experienced team of researchers who met regularly with the research student. Any reflections or changes to the study as a result of these meetings were well documented and recorded.

Confirmability

"Confirmability evaluates the extent to which findings are qualitatively confirmable through the analysis being grounded in the data and through examination of the audit trail."(Hannes K et al. 2011). This was confirmed by the transparent reporting of the coding process as per Appendix 7. LB frequently reflected on how the data was interpreted with reference to her own position and regular notes were taken at meetings. Versions of transcripts including tracked changes were saved so it was possible to follow the process of analysis. Evaluation techniques include: assessing the effects of the researcher during the steps of the research process, reflexivity, the researcher's background, beliefs and assumptions (Hannes K et al. 2011). The concept of confirmability is the investigators objectivity; steps should be taken to ensure that the study's findings are the results and experiences of the participants rather than characteristics of the researcher (Shenton 2004). This was assessed by reflecting on LB's position as the researcher, background, position, seniority, education and reflexivity.

4.9 Results

The study was designed to assess whether using the LAAT gave more consistent results in the assessment process. Table 4.4 shows the results from the consensus groups compared to the 'gold standard' (GS) it shows that some cases lead to complete agreement. Other cases lead to wide divergence. This includes some assessors saying definitely avoidable and others saying unavoidable. There is also complete agreement and complete divergence between assessors and gold standard.

Table 4.4 Avoidability category assignments of consensus groups – a comparison to the gold standard

ADR Type	Gold standard avoidability	Consensus group 1	Consensus group 2	Consensus group 3
Vomiting	Definitely avoidable (AH chemo N+V)	Not avoidable	Not avoidable	Not avoidable
Procedural vomiting	Definitely avoidable (AH PONV)	Definitely avoidable (AH PONV)	Definitely avoidable	Definitely avoidable
Somnolence	Definitely avoidable	Not avoidable	Not avoidable	Possibly avoidable
Immunosuppressant drug level increased	Definitely avoidable (BNFC)	Definitely avoidable (BNFC/looked for tacrolimus guideline)	Definitely avoidable (BNFC)	Definitely avoidable (BNFC)
Constipation	Definitely avoidable	Definitely avoidable	Definitely avoidable	Not avoidable (AH NCA/PCA)
Hallucination	Not avoidable	Not avoidable	Definitely avoidable (BNFC)	Unassessable (BNFC)
Cardiac failure	Possibly avoidable	Not avoidable	Not avoidable (SPC)	Not avoidable (SPC)
Respiratory depression	Possibly avoidable	Definitely avoidable	Definitely avoidable	Possibly avoidable (AH NCA/PCA)
Flushing	Not avoidable	Possibly avoidable (BNFC)	Possibly avoidable (BNFC)	Not avoidable (SPC + BNFC)
Pruritus	Not avoidable (AH NCA/PCA)	Definitely avoidable	Definitely avoidable	Definitely avoidable AH NCA/PCA
Visual disturbance	Not avoidable	Not avoidable	Not avoidable	Not avoidable (BNFC/AH PCA)
Diarrhoea + Excoriation	Not avoidable	Definitely avoidable	Definitely avoidable	Possibly avoidable
Hypocalcaemia + Hypophosphataemia	Not avoidable (BNFC)	Possibly avoidable	Not avoidable (SPC)	Not avoidable (SPC)
Haematemesis	Not avoidable	Unassessable	Possibly avoidable	Not avoidable (checked intranet for guideline- none found)
Hypertension	Not avoidable	Definitely avoidable	Possibly avoidable	Definitely avoidable
Infusion associated reaction	Not avoidable (BNFC)	Not avoidable (BNFC)	Not avoidable	Not avoidable
Urinary retention	Not avoidable	Not avoidable	Not avoidable	Not avoidable (AH NCA/PCA)
Clostridium difficile colitis	Not avoidable	Not avoidable	Unassessable	Not avoidable
Stomatitis	Not avoidable	Not avoidable	Not avoidable	Not avoidable
Hypoglycaemia	Possibly avoidable	Not avoidable	Not avoidable	Definitely avoidable
% Agreement	-	45%	40%	55%
No. of guidelines consulted	6 (3 x BNFC, 3 x AH)	4 (3 x BNFC, 1 x AH)	5 (3 x BNFC + 2 x SPC)	11 (4 x BNFC, 5 x AH + SPC x 2)
% Avoidable	40%	45%	50%	42%

The study aimed to explore factors that influenced decision making in the MDT consensus meetings and to review group processes, such as turn taking, during meetings. Table 4.5 outlines the differences between the three consensus groups the information contained in the table was taken from summary data from the meeting observations recorded by LB.

Table 4.5 Differences between the three consensus groups:

Consensus Group	Rapport	Group member participation	Use and understanding of the LAAT	% of cases where guidelines were consulted
Consensus group 1	Excellent group rapport	All group members participated fully.	Quickly grasped the concept of the tool and how to use it. Good understanding.	20%
Consensus group 2	Good group rapport (took slightly longer to establish)	Worked mainly as a group but the pharmacist seemed to take the lead.	Initially struggled to understand the central boxes. Required more clarification from the facilitator.	25%
Consensus group 3	Good group rapport	All group members participated. Worked well together.	Overall good understanding of the tool	45%

The study aimed to review the use of guidelines during MDT consensus meetings. From the meeting observations it was clear that there was a difference in the attitude and use of guidelines within professions but there was also a difference in practice observed between the three consensus groups. Consensus groups 1 and 2 had a similar approach to the use of guidelines and consulted them for 20 and 25% of cases respectively. There was a noticeable difference in the approach taken by consensus group 3 they consulted guidelines for 45% of cases. Guidelines were consulted in the 'gold standard' consensus meetings for 30% of cases.

Interviews

Eight out of nine group members took part. It was not possible to interview the ninth member due to scheduling arrangements as a large time period elapsed before an interview was possible at which point it would not have been practical to have conducted the interview. All the interviews were audio recorded and transcribed verbatim. The interviews ranged from 6 to 21 minutes in length with a mean time of approximately 11 minutes. Table 4.6 shows the details of the interviews and background of the interviewees.

Table 4.6 Details of the post consensus meeting interviews

Clinician type	Specialty	Grade/number of years' experience	Consensus Meeting Date	Date interviewed	Location of interview	Duration of the interview
Doctors						
GD1	Endocrinology & Diabetes	ST5 or above	04/02/2014	04/02/2014	Consensus meeting room	13 min
GD2	A&E rotation	ST4 or below	10/02/2014	10/02/2014	Consensus meeting room	6 min
GD3	Oncology	ST5 or above	26/02/2014	27/02/2014	LB's office	10.15 min
Nurses						
GN1	Oncology/ Research nurse	> 10 years	04/02/2014	04/02/2014	Consensus meeting room	9 min
GN2	Medical/ Research nurse	>10 years	10/02/2014	10/02/2014	Consensus meeting room	11 min
GN3	Oncology/ Research nurse	>10 years	26/02/2014	26/02/2014	LB's office	6.06 min
Pharmacists						
GP1	Specialist paediatric clinical pharmacist	<10 years	04/02/2014	05/02/2014	LB's office	21.21min
GP2	Specialist paediatric clinical Pharmacist	>10 years	10/02/2014	11/02/2014	LB's office	12.43 min
GP3	Specialist paediatric clinical pharmacist	>10 years	26/02/2014	n/a	n/a	n/a

The format in which the findings are presented broadly reflect the key themes we developed during the course of the analysis. We first describe clinicians' awareness of ADRs and the terminology used. We then describe the clinicians' experience of using the tool. Finally, we describe the clinicians' thoughts and experiences of being part of a MDT group for case assessment. Some key themes which emerged from the interviews and observational data are outlined below.

4.10 Key themes

Conceptual awareness

Clinicians generally reported poor awareness and experience of ADRs and recalled relatively mild and common ADRs: *"Oh gosh you know diarrhoea with antibiotics, constipation with codeine, all the sort of common ones, rashes with antibiotics"* (GD2). Clinician's accounts of their experience of ADRs also suggest there is confusion around terminology, especially around ADRs, ADEs, medical errors and side effects:

Could I describe [pause] ehm many platelet reactions, blood transfusion reactions, lots of itching or hives, swollen lips post drugs. When some of the kids have had stem cell transplants some of the reactions there as well. Even with having piriton and hydrocortisone before and yeah still (GN1).

There was also some confusion over the terms causality and avoidability. An example of this is highlighted below by the quote from GD3 where they are talking about causality rather than avoidability. However, despite this comment in the post consensus meeting interview it did not appear to impact on the ADR assessments. At the beginning of each consensus meeting the overview provided by the facilitator highlighted that the purpose of the meeting was to assess avoidability only and that each ADR case report already had a causality assessment completed and all the ADRs were deemed either probable or definite.

I certainly think it has got a lot of potential. I think it has got quite a lot of potential in trials for example, when you are looking for novel or in turn long-term pharmacovigilance and I think if there is something like that then there are kind of unexpected side effects and things (GD3).

Perceptions of the tool

Clinicians were generally positive about the tool and could see how it could be used in practice:

So say if you were getting lots of possibly avoidable then you could say well actually we've looked at 50 children, pretty much all of these under 5s do get constipated, let's put on our morphine sticker, prescribe a laxative and it solves the problem [...] Using this tool you could then use it to improve things next time in the future so I think that's good (GD1).

And also in research: *"Yeah a research tool" (GD2).*

One clinician also described how the tool could possibly be adapted for use in reviewing medical errors:

I'm obviously involved in review for errors and so on. I suppose you could maybe could start thinking about how could that error be prevented, could that error be prevented or not and it would require some adaptation but ehm (GP2).

Another clinician felt that using the tool focused the mind to process information in certain logical way and that this was helpful: *Yeah, it makes you take it apart really, you know have a look at it in quite a strategic way. So yeah, I think it is really helpful. (GN2).*

An unexpected finding was that one clinician felt the tool promoted self-reflective practice: *"It's a good tool to use to assess your own practice. So if there is an incident where a patient becomes unwell you can sit and think let's have a look at this" (GP1).*

Comments on the tool itself or regarding specific boxes on the tool:

Overall clinicians were positive about using the tool and its ease of use. However, there were some comments about box 3 and the central box on the LAAT: “Were there known preventative strategies and/or appropriate management plan(s) with information about ADR avoidance available?” and “Were other information sources, or information in the history available for the prevention of the ADR which could have been followed?”

“Yeah I think it’s easy to use” (GD1) “Yeah, it was nice and simple, and looking at it now, it’s like a clear diagram isn’t it. Initially you’re not put off when you first look at it. I think there were just those two questions wasn’t there” (GP2).

Well I think it’s very good, I think as we were saying before, this third box the preventative strategies it’s just working out the kind of context of the scenario and kind of [02:25:00] I think the way it flows is very good and I would be happy kind of using that in the future for other things, it’s well devised (GN1).

Yeah I think it was really helpful. I do think it would be useful, it was just that third box that even towards the end, when we were used to using the tool, it got me every time really. Yeah just a bit confusing but it just takes longer to think about it [...]yeah you just have to stop and think about it whereas, the start of the tool is straightforward (GN2).

In reference to the tool’s glossary and reading of information; *I suppose I didn’t really read that properly [laughs] so that’s why so yeah (GD1).*

A suggestion was made by the pharmacist in consensus group 3 about how the tool could possibly be improved by the addition of “[...] modification to include consideration of ADR and deliberate decision to proceed in a certain course of action” (GP3)

Perceptions of groups versus individuals

Clinicians were generally positive about assessing cases within a group and could see a number of advantages to working within an MDT. Clinicians especially valued access to expertise: *“Yeah I think come to similar conclusions but I think it is easier with the group [laughs] yeah especially with a pharmacist. I think it would take me a lot longer on my own to be honest” (GD1).*

Observation data from consensus group 1 showed that all members contributed to the discussion and there was frequent request for confirmation and agreement for each other. Members especially deferred to others where there was a specialist e.g. pharmacists for medicine safety or guidelines for example there were several examples of both the doctor and nurse looking to the pharmacist for clarification regarding doses, guidelines and what was standard practice.

For example, in one case: ADRID 2103 - the patient has a raised tacrolimus level after receiving clarithromycin. In consensus group 1 the doctor and nurse asked the pharmacist what the normal levels should be for tacrolimus, whether clarithromycin was contraindicated and if there were any guidelines. The pharmacist responded and there was good group discussion over the case in group 1. Interestingly, in the other two consensus groups (groups 2 and 3) it was the pharmacist who was asked about what the normal levels of tacrolimus should be and whether any guidance exists specifically for transplant patients.

In another case ADRID 477; the patient was receiving prednisolone as part of the ICISS trial and they developed hypertension. In consensus group 3 the nurse had experience of working on the ICISS study and therefore shared her knowledge with the team regarding blood pressure measurements and their frequency. The other group members responded well on hearing that GN3 had experience of the ICISS study and asked her to share her knowledge of the study protocol and the group then deferred to GN3's experience and familiarity with the study.

During the consensus meeting observations there were a couple of cases involving particular specialties for example oncology or cardiology where hesitation and uncertainty were observed amongst the group. For example, ADRID 2105 - cardiac failure related to bisoprolol caused a lot of discussion amongst the groups. A number of group members stated they were not very familiar with the area. It was noted that there was uncertainty over where to access information about bisoprolol. In consensus group 1 and 2 the pharmacists recognised immediately that it would not be listed in the BNFC as it is not licensed for children and therefore both suggested looking up the SmPC instead. The groups all had lengthy discussions about the case and each member contributed to reaching consensus decisions. Feedback from the post consensus meeting interviews showed the value of MDTs and reliance on colleagues for guidance on areas which were unfamiliar. A quote from the post consensus meeting interview with GN2 highlights the value of an MDT; in response to being asked about whether they would have reached the same conclusions on their own.

Erm, possibly not for a couple of them possibly ehm because other people have, so for the cardiac one, I'm not familiar with the cardiac medications and the pharmacist obviously was, so no for a couple of them I possibly would have struggled (GN2).

Yeah, I think especially with the one, I think it was the mucositis or the oncology one. We were almost at a conclusion until the pharmacist mentioned something and it took us right back to the beginning and that led us to think that it was unassessable that ADR because you know we needed more information from the previous reaction. Yeah, definitely yeah (GN2).

Clinician's accounts reinforced the observational data and suggest that they perceive the expertise in MDTs could help overcome poor use of guidelines: "We as doctors very rarely look at all the kind of product information, the EMC and the EMI lists and things and probably not as aware of many of the hospital guidelines for example" (GD3). "I think finding the guidelines in this hospital is quite hard isn't it?" (GD1).

Instead, clinicians reported relying on their own knowledge and experience: *“I kind of know in my head what I’m supposed to do [...] (GD1). Possibly as a result, clinicians especially valued the contribution of expertise into the decision making process: “And it is how you interpret what this management plan or guideline is, especially if it isn’t a fixed guideline and so it was quite helpful having an endocrine person there” (GP1).*

Yeah, it works quite well as a group [...]people brought their experience from- for example the pharmacist was very much kind of looking at the pharmaceutical information, the pharmacy information and basically looking at the BNF [...] So I think when you’ve got the three kinds of reference points it is easier[...]. So it’s quite good that you have that triangulation (GD3).

The observation data showed that in consensus group 1 and 3 it was both the pharmacist and doctor who consulted the guidelines. In consensus group 2, it was mainly the pharmacist who looked up any guidelines.

Some clinicians also reported feeling that working within a multidisciplinary team overcame feelings of blame and judgement:

It’s just really interesting that in some situations we have wanted to get away from saying it was an avoidable drug reaction [...] but actually being able to say yes it was avoidable, but that doesn’t mean that anyone was at fault or we’ve done anything wrong. That was just quite an interesting thing (GP1).

Balancing judgements

In all three consensus meetings there was evidence of balancing judgements observed where group members looked to each other for confirmation and reassurance. Clinicians reported that making decisions within a group helped reduce the chance of missing something and also was very helpful for certain areas or specialities that people were less familiar with as outlined above in the cardiology and oncology cases. It was noteworthy in the post consensus meeting with GN3

where upon being asked about any potential disadvantages to working in a group she responded with *"Yeah, I think if somebody was very strong I think it would be a little bit difficult, but I think it's about being able to put your views forward"*. When GN3 was asked about being in a group:

Yeah, I did think it worked well because I think if you've got the mix of people from different areas erm, it gave a good background of knowledge and I think having a pharmacist, doctor and nurse I think it was, it had different viewpoints, yeah" ... "I think if you were doing it on your own you wouldn't question some of the thoughts and everything that some discussion needs to be done, especially in some of the areas that you wouldn't specialise in and you don't 100% know about those. Yeah, I think definitely a group (GN3).

There was evidence from the meeting observations of group discussion and post meeting interviews found participants were positive about working as a group. *"I think if you were doing it on your own you wouldn't question some of the thoughts [...]some discussion needs to be done, especially in some of the areas that you wouldn't specialise in."* (GN3). *"Yeah of course, it also means that someone might spot something that you didn't see"* (GP1). *"I think it is useful to bounce ideas because you can convince yourself of things can't you? It's good to do it as a group"* (GD1).

A small number of clinicians reported some concerns; especially that the MDT could prevent a team from reaching consensus:

I think the only thing is that you can have quite different perspectives on stuff can't you, for example, the oral one yesterday you can get a bit bogged down on semantics and just individual words and things, but I think there is a bit of flexibility in the tool. I think the ones that two middle boxes are the ones where you can get to different routes, kind of allows for that though (GD3).

Or that some clinicians may dominate discussions: *"I think ehm, somebody who wasn't as confident to speak out, possibly be a disadvantage. Would they challenge somebody who is more out spoken"* (GN3).

Disagreement and agreement

Overall the three consensus groups worked well together to reach a consensus opinion. However we observed a couple of examples of disagreement particularly in consensus meeting 3. Strong views on certain cases by some individuals led to disagreement. This included ADRID 1294 – constipation: there was some debate mainly between the pharmacist and doctor regarding the action taken; as no prophylactic laxatives were prescribed. Although there is very limited guidance available, the 'gold standard' for this case was 'definitely avoidable' and it was also the outcome reached by the other two consensus groups. In the end the outcome reached by consensus group 3 was 'not avoidable'. *"I think that is a fairly difficult one because not everyone gets it and you're not going to start prophylactic laxatives on someone who getting opiates on ICU"* GD3.

A quote from the pharmacist highlighted their unease with the assessment: *I'm struggling with that one because I think everybody knows that opiates can constipate and people have been a bit quicker given that he hadn't opened his bowel since admission and he was admitted when [.....]* GP3.

There was some discussion over whether there were any available guidelines and the Trust's PCA guideline was consulted. The dialogue between the pharmacist and doctor continued and in the end they answered yes to "were there known preventative strategies and/or appropriate management plan(s) with information about ADR avoidance available?" and then by answering yes to "were the strategies and/or management plan (s) followed it took them to 'not avoidable'.

GP3 *So your clinical knowledge would steer you in that direction*

GD3 *So, and I think they have been followed*

GP3 *And they've been followed?*

GD3 If I saw this child on HDU over a weekend I would be fairly happy with what's gone on and when it's been recognised it's been addressed fairly quickly, it's been treated

GP3 So in that case that would come out as a not avoidable because the strategy and management plan were followed, that doesn't feel comfortable to me

GD3 No, it's a possibly avoidable isn't it

GP3 Yeah

GN3 Yeah

GD3 Because I think just with kind of rigidity of those four outcomes it has to go the other way unless you can actually audit through the notes and see what decisions were made and at what point

GP3 Ok, so in changing our minds to say there were preventative strategies, we have taken ourselves through to not avoidable

The vomiting related to chemotherapy case was an example of complete divergence from the gold standard. All three consensus groups categorised the ADR as not avoidable whilst the gold standard assessment was definitely avoidable. Interestingly, none of the consensus groups consulted the guidelines. The gold standard consensus group consulted the local guidance on prevention of nausea and vomiting related to chemotherapy. Although some antiemetics had been given prophylactically the chemotherapy the patient received was categorised as high emetogenic risk and according to the guidelines could therefore have been given additional antiemetics. From the meeting observations it was noted that all three groups felt some preventative strategies had been taken and the discussion amongst the groups was relatively brief and a decision was reached quickly. Two of the groups made reference to the existence of a guideline but chose not to consult it. The pruritus case again was an example of complete divergence from the gold standard and guidelines were only consulted by consensus group 3. From the

meeting observations this case highlighted some difficulty or confusion between prevention and management. Consensus group 2 also showed consideration of severity in the assessment and they appeared to be confused between the subtle difference between prevention and management. They talked about how the ADR could have been avoided sooner, the severity of the itching and the interventions made by the team which are all valid points but not actually related to avoidability. In order to avoid the ADR in the first place chlorpheniramine would have had to have been given alongside the fentanyl which is not standard practice. The guidelines suggest giving chlorpheniramine if the patient develops pruritus.

4.11 Discussion

Overall clinicians gave positive feedback about using the tool and saw potential for its use, but there was some confusion about concepts and terminology that may need addressing. The impact of the confidence and competence of using clinicians with varying levels of experience may have impacted on the IRR. This may reflect wider deficits in the knowledge of clinicians and it highlights the need for additional training. These issues could possibly be addressed by the introduction of extra teaching and training sessions. We might have expected the groups to have performed better than the individuals given the perceived advantage of having a MDT input. The impact and advantage of group MDT assessments might have been more noticeable in a more experienced group. The lack of experience of some reviewers perhaps reduced their ability to contribute to the discussion.

Clinicians generally liked using the tool in an MDT situation and felt it speeded up decision making, promoted more balanced decisions, reduced feelings of blame and judgement and could offset the lack of, or lack of use of guidelines because of expertise in MDT meetings. Key themes and concepts which emerged from the study included conceptual awareness, perception of the tool, perception of groups versus individuals and the use of guidelines. People make choices about which information to look at and then make decisions with that information. During the consensus groups I observed differences in practice, with some clinicians choosing

to look up guidelines and reference sources and others not looking at any information instead relying on their previous knowledge or the knowledge of others. There was variation in patterns of thinking between the groups with some groups not looking up any guidelines and instead deferring to colleagues for confirmatory purposes rather than contradictory. A survey conducted in the US to investigate the attitudes and usage of clinical practice guidelines found that guidelines were used by 35% of paediatricians, 44% reported using them in part and 21% reported they did not use guidelines (Flores et al. 2000). This is similar to our own findings where guidelines were consulted in just over 30% of cases.

There was also variation in team members' role and level of participation in discussions depending on their profession; overall the doctors and pharmacists appeared to take the lead more in discussions however, there were also examples of nurses taking a more central role particularly in consensus group 1 and on certain occasions in consensus group 3, for example the hypertension case where the nurse in group 3 had worked on the study and was familiar with the study protocol. The other group members deferred to the nurse and asked questions about the frequency of monitoring and information contained in the ICISS protocol. Examples of familiarity were also seen with the cardiology and oncology cases. In the cardiology case for example, the pharmacist was familiar with the suspected medicine, bisoprolol and was aware that it would not be listed in the BNFC and knew to consult the SmPC for information regarding the contraindications and was able to share this information with the team in order to facilitate the decision making process.

Clinicians were generally positive about using the tool but there was some confusion about concepts and terminology that may need addressing as this has been shown to have implications for practice, especially in multidisciplinary practice (Gandy, Kershaw & Beaumont 2002). The consensus groups consulted more guidelines than the individuals (or at least those individuals that specified if guidelines were consulted) particularly consensus group 3 as outlined in Table 3.3

Chapter 3. Agreement with the 'gold standard' was similar for individuals and groups. In terms of %EA individuals had marginally better agreement with the 'gold standard' than the consensus groups. Given the logistic difficulties with groups, individual assessments may be preferable but we have shown that both methods are possible. Similar to the study by Kidger et al. (2009) there was some variation in participation by different professions seen particularly in consensus groups 2 and 3. In group 2 the pharmacist (GP2) seemed to take the lead role and in group 3 the doctor (GD3) and pharmacist (GP3) appeared to have more dominant roles, although the nurse (GN3) contributed well and played a central role in some cases (Kidger et al. 2009). The seniority effect where group discussions were dominated by senior consultants seen by Kidger et al. (2009) was not seen in this study. Overall, in this study each group member participated in the discussions and consensus opinion was reached. This study showed that group members deferred to specialism within the MDT rather than seniority which may be as a result of the diverse group brought together for the purpose of this study one that would not necessarily be reflected in real life where a team would be made up of specialists and would, in that case defer to seniority. There were no pharmacists involved in the MDT in the study by Kidger et al. (2009). The three differential pathways and outcomes of discussion reported by Kidger et al. 2009 were similar to those observed in this study (Kidger et al. 2009).

A potential study limitation was that the presence of the observer and facilitator may have affected the decision making process. However, in reality this did not seem to be a problem perhaps because the volume of cases to be assessed in a limited time period meant the effect of the observer was lessened. Other possible study limitations were the small numbers and number of groups due to practical issues and feasibility, the artificial environment and the way in which study participants were selected and assigned again due to practical issues and availability to attend consensus group meetings.

The study was designed to assess whether using the LAAT gave consistent results. Quantitative data and analysis suggests variation in outcome. This variation can

occur for a number of reasons and variation in outcome may, or may not, arise from variation in process for example how people assess avoidability and the use of guidelines. Using qualitative tools different approaches to avoidability assessments were observed. The consensus groups were more inclined to attribute a 'definitely' or 'possibly' avoidable assessment to the cases than the individuals. For some cases there was complete agreement between the three consensus groups but disagreement with the 'gold standard'. Consensus group 3 had the best agreement with the gold standard and they also looked up more guidelines than the other two groups. Consensus groups 1 and 2 looked at guidelines less frequently and observations suggest that they relied more on tacit knowledge, familiarity and recall.

Some of the variation between gold standard and group assessments may have arisen because the study team made some assumptions during the development and testing of the LAAT. The study team developed and followed a set of 'rules' for using the tool to assess the avoidability of ADR cases. Different interpretation of those 'rules' by other groups/individuals may be a reason for different outcomes of the assessment. Failure to consult guidelines that may be appropriate is one good example of not following the 'rules'. Given additional instruction or training about the rules the agreement between assessors might be closer. Potential ways to overcome this might include producing more guidance on the use of the tool. However, we were reluctant to do this for two reasons: 1) ideally the tool should be useable without too much instruction and 2) we were aware that often people will not read the accompanying information as we witnessed in this study. Therefore, additional training on the use of the tool is potentially a better way of improving agreement and would be more likely to be effective. Strengths of the study include positive feedback from participants on the use of the tool and comments which reflected the potential utility of the tool in the future.

During discussion about the results it was found that some of the findings resonated with the concept of heuristics. Heuristics are 'efficient cognitive processes, conscious or unconscious that ignore part of the information with the goal of

making decisions more quickly, frugally, and/or accurately than more complex methods' (Gigerenzer and Gaissmaier, 2011). Research indicates that individuals and organisations often rely on simple heuristics in an adaptive way (Gigerenzer, Gaissmaier 2011). Simon (1957) showed that we operate within what he called 'bounded rationality'. It has been shown that ignoring part of the information can often lead to more accurate judgements rather than weighting and adding all information. When making a decision, there is so much potentially relevant information available, it is impossible to know or process it all (so called 'bounded rationality') (Simon 1957). He coined the term 'to satisfice', where people seek solutions or accept choices or judgments that are 'good enough' for their purposes, but could be optimised (Simon 1957). Usually, a limited amount of information is selected to reach a sufficiently satisfactory decision, this process known as satisficing. Findings from a study which looked at clinical decision making in practice were consistent with the theory of bounded rationality which provides plausible explanations for a physician's ability to make intelligent choices quickly and with minimum necessary information (Ribeiro Bonilauri Ferreira et al. 2010).

During the analysis the value of heuristics emerged as a useful meta-theme. Looking at how people assess avoidability showed that people use familiarity and tacit knowledge more often than consulting official guidelines. The use of multidisciplinary groups could offset some of this variation. Heuristics may be one way that people make choices and one way of assessing variability. Heuristics can be structured and improved in contrast to convenient "rules of thumb". In fact, the LAAT may itself be viewed as a heuristic that promotes structured reasoning.

While some avoidability assessments may appear to be inherently variable and subjective this does not preclude the use of a tool. Discussions within groups or structured assessment by individuals are useful. Clinical actions to avoid ADRs may be identified even if avoidability classification differs. The findings of variability between assessors and groups raised the question of whether a more standardised approach to assessments should be taken. After much consideration it was agreed that in practice this would be very difficult to implement. As despite detailed

guidance on the use of the tool and how to interpret the questions in this study we observed how infrequently this was consulted and in many cases it was not used at all. Providing guidelines may not work as we observed that people rarely used them. More research is needed on how people make decisions in real life situations. For example do they consistently consult other colleagues within a specialism or do clinicians defer to seniority as in Kidger's study (Kidger et al. 2009).

4.12 Conclusion

Overall the findings in this study were similar to those of Kidger et al. (2009). In this study, on average guidelines were consulted for just over thirty percent of the cases. Overall it appeared that reviewers relied on tacit knowledge and experience (either their own or others) than on guidelines and this may have implication for the generalisability of the study findings and also who should/could use the tool (for example is there a threshold of experience that is needed before using the tool effectively?). The research undertaken in Chapters 3 and 4 has shown that a mixed methods approach was justified and consistent with the research questions. The benefit of a mixed methods approach has been the rich data generated through the interviews and consensus groups which could not have been gathered otherwise. The qualitative data complements the quantitative data and perhaps begins to explain the results found during the quantitative research.

The meeting observations and post-consensus meeting interviews have helped to explain possible reasons for variation in outcome of results and the observed differences between the three consensus groups and the gold standard consensus group. We have observed in practice that groups were reluctant to look up guidelines and information this may have implications for how the tool is used in the future. Further work could be carried out to optimise group assessments and use of the tool. However, the tool has also been shown to be used effectively by an individual as described in Chapter 5. The tool designers developed and followed a set of rules and if those rules are interpreted differently by groups or individuals

this may explain some of the observed differences. The provision of additional instruction or training about the use of the tool might help improve agreement.

Chapter 5: Avoidability assessment of the ADRIC admissions study cases using the LAAT and a comparison to existing Hallas scores

5.1 Introduction

As outlined in Chapter 2, there have been many attempts to devise tools or scales to help determine avoidability. Commonly used scales include, Hallas (1990) and Schumock and Thornton (1992) which are based on appropriateness of prescribing or treatment choice. The Hallas scale (1990) was used for the ADRIC admissions study but it quickly became clear that it was not suitable for the ADRIC inpatient study due to difficulties encountered particularly, around the terminology used, as discussed in detail in Chapter 2. As a result of this, it was decided by the study group that we would design a new AAT which would be more applicable for use in paediatrics but could also be used in other settings. Ideally, the newly developed tool should be reproducible, easy to use and generalisable to a variety of different patient groups. Hakkarainen et al (2012a) recommended that any new avoidability instruments should be compared to existing ones. Therefore, we compared the newly developed LAAT to the Hallas scale (1990) which was used to assess avoidability in the ADRIC admissions study (Gallagher et al. 2012) by comparing the results of the avoidability assessments for both tools.

The ADRIC admissions study was a prospective observational study carried out over a one year period (1st July 2008 to 30th June 2009) which looked at ADRs causing admission to hospital. During the study period, there were 8345 admissions. The estimated incidence of admissions due to ADRs was 2.9% (249) (Gallagher et al. 2012). Of the 249 ADRs in the study 120 of them were oncology related (48%). The Hallas scale (1990) was used to determine avoidability via a consensus method. Gallagher et al. (2012) found that 78% of ADRs were unavoidable, and 22% were either possibly or definitely avoidable. Gallagher et al. (2012) suggested some potential prevention strategies for ADRs based on their assessment of the ADRs they classed as 'definitely avoidable': that more careful attention to practical

aspects of care, such as improved monitoring, following prescribing guidelines and improved patient education could lead to a reduction in the frequency of ADRs causing admission.

5.2 Aim

To assess the avoidability of the ADRIC admissions study cases using the newly developed Liverpool avoidability assessment tool and to compare the results to the existing Hallas assessments carried out as part of the ADRIC programme.

Objectives

- To examine the agreement between the LAAT and Hallas assessments
- To identify the types of ADRs that may be avoidable

5.3 Methods

All 249 ADR case reports identified during the ADRIC admissions study were individually reviewed by one person (LB) using the LAAT to assign an avoidability outcome for each case. The pathway taken on the LAAT for each case was recorded and any guidelines consulted were noted. In addition if a case was classified as 'possibly' or 'definitely avoidable', the rationale for the perception of avoidability was recorded. The case reports contained anonymised demographic data for the affected patient, details of suspected and concurrent medication, past medical history, and a description of the adverse reaction, treatment and outcome. After all the assessments with LAAT had been completed the LAAT assessments were compared to the Hallas scores previously assessed as part of the admissions study via a consensus method (Gallagher et al. 2012). Categorical scores for both the LAAT and the Hallas scale use the same four point ordinal scale: 'Definitely avoidable', 'possibly avoidable' 'not avoidable' or 'unavoidable' and 'unassessable' or 'unevaluable'.

Validation

For quality assurance purposes a purposive sample - 10% of cases (25) were assessed by a second reviewer- senior investigator (MT).

Analysis

A descriptive analysis for all ADRs in the sample was conducted. The ADRs were counted according to their classification: definitely avoidable, possibly avoidable, not avoidable, or unassessable. The avoidability categories assigned using the LAAT were compared to the Hallas assessments (Gallagher et al. 2012).

The overall agreement for LAAT assessments and Hallas assessments were summarised using descriptive statistics, means with 95% confidence intervals alongside the exact agreement statistics. Exact agreement percentages were computed to measure the absolute concordances between assessor scores that is the percentage of cases that were given the same category in the two assessments. The percentage of extreme disagreement (%ED) where the avoidability scores between the two raters of the same case are wider than one interval apart was classed as extreme disagreement; for example a case classified as definitely avoidable by one rater and not avoidable by the other. Kappa values were interpreted according to the guidance from Altman (1991) as per Chapter 2.

Ethics approval

This study was part of a larger study which used routinely collected clinical data in an anonymised format. The Chair of Liverpool Paediatric Research Ethics Committee (REC) issued a formal opinion that the larger study did not require individual patient consent or review by an Ethics Committee. The planned analysis required routinely collected patient data and was therefore classified as an audit.

5.4 Results

Assessment of the 249 ADR case reports using the LAAT found that 19.3% were either possibly or definitely avoidable (Table 5.1). This was similar to the Hallas results where 22% of the reactions were either possibly or definitely avoidable (Gallagher et al. 2012). Of the 120 (48%) oncology related ADRs 7 were classified as avoidable: 4 as possibly avoidable and 3 as definitely avoidable. Of the three 'definitely avoidable' cases, two were vomiting related and one was constipation related. Three of the possibly avoidable cases were related to constipation where two were attributable to vincristine and ondansetron and one had dihydrocodeine, all without laxative prophylaxis. The fourth possibly avoidable ADR was a gastritis case related to dexamethasone. Of the 129 non-oncology cases 41 were classified as avoidable: 36 as possibly avoidable and 5 as definitely avoidable.

Overall percentage exact agreement (%EA) was 90%; when subcategorised into oncology and non-oncology cases the %EA was found to be 94.2 and 86% respectively. %ED was 0.8%. The two cases with extreme disagreements were oncology cases (Tables 5.1 and 5.2). The kappa score was 0.71 (95% CI 0.60 - 0.82) for all cases, 0.54 (95% CI 0.40 - 0.68) for the oncology cases and 0.73 (95% CI 0.58 - 0.88) for the non-oncology cases. Overall there were 25/249 cases with disagreement, shown in Figure 5.1. In total there were 48 cases that were categorised as either possibly or definitely avoidable. The cases and the reasons for their categorisation are summarised in Table 5.3.

Table 5.1 Avoidability of ADRs oncology versus non-oncology

ADR Type	Hallas Avoidability Count of ADRs (%)			LAAT Avoidability Count of ADRs (%)		
	Unavoidable	Possibly avoidable	Definitely avoidable	Unavoidable	Possibly avoidable	Definitely avoidable
Oncology (n=120)	112 (93.3)	6 (5)	2 (1.7)	113 (94.2)	4 (3.3)	3(2.5)
Non - oncology (n =129)	82 (63.6)	39 (30.2)	8 (6.2)	88 (68.2)	36 (27.9)	5(3.9)
Overall (n= 249)	194 (77.9)	45 (18.1)	10 (4)	201 (80.7)	40 (16.1)	8(3.2)

Table 5.1 shows the comparison of avoidability categories for Hallas compared to the LAAT overall and in terms of oncology and non-oncology breakdown.

Figure 5.1 ADRs with disagreement oncology versus non-oncology

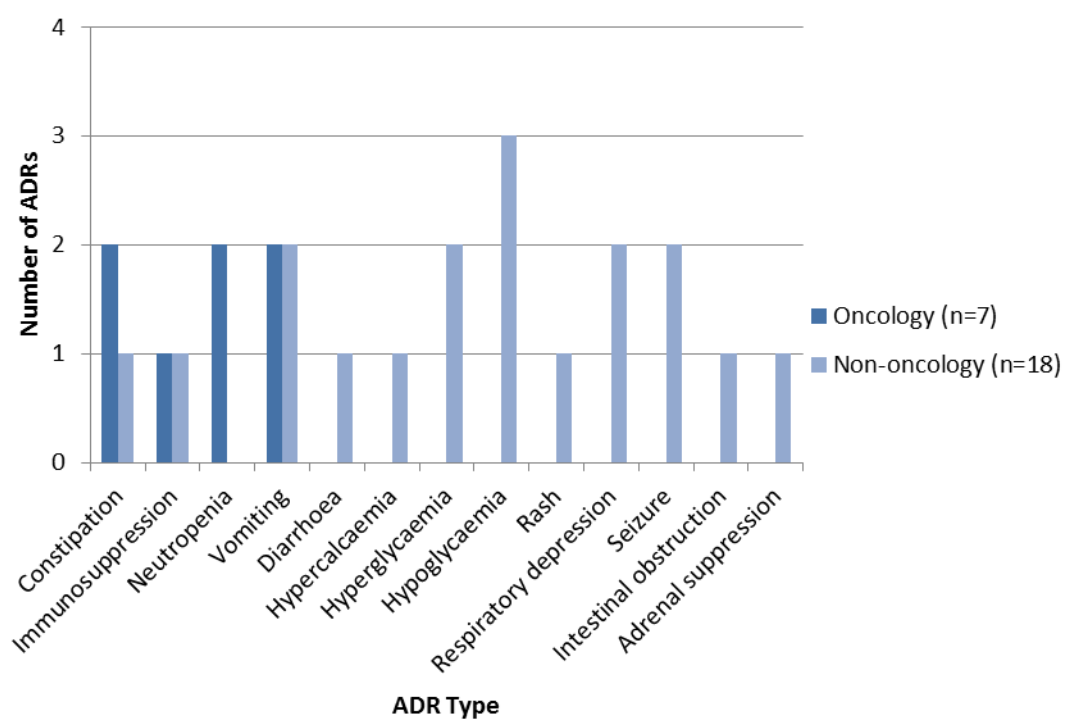


Figure 5.1 shows the ADR cases where disagreement occurred between Hallas and the LAAT and the breakdown in terms of oncology and non-oncology cases.

Table 5.2 Breakdown and overall agreement between Hallas and LAAT

ADR Type	Hallas assessment versus LAAT assessment	
	Agree	Disagree
Oncology (n=120)	113 (94.2%)	7 (5.8%)
Non-oncology (n= 129)	111 (86%)	18 (14%)
Overall (n= 249)	224 (90%)	25 (10%)

Table 5.2 shows the overall agreement between Hallas and the LAAT and the breakdown of oncology and non-oncology cases.

Table 5.3 Possibly and definitely avoidable ADR cases and rationale for assessment

Avoidable	Frequency	ADR Type	Drug Classes	Reason for potential avoidability
Definitely	1	Constipation	Opioid analgesics, Cytotoxics	No prophylaxis given
Definitely	1	Deranged Renal Function	Drugs affecting the renin-angiotensin system	Frequency of monitoring
Definitely	1	Diarrhoea	Antibacterial	Appropriate indication for antibiotics signs/symptoms of viral illness?
Definitely	1	Hypoglycaemia	Drugs used in diabetes	Avoidable with improved patient education – for example insulin use when unwell. Patient had a past history of the same when unwell previously.
Definitely	2	Immunosuppression	Corticosteroids, Drugs affecting the immune response	Frequency of monitoring of drug levels
Definitely	2	Vomiting	Cytotoxics	Post chemo vomiting - appropriate antiemetic prophylaxis used?
Possibly	1	Adrenal suppression	Corticosteroids	Frequency of monitoring
Possibly	1	Intestinal obstruction	Anti-motility drugs	Avoidable with improved patient/parent education
Possibly	1	CNS depression	Opioid analgesics	Monitoring for drowsiness
Possibly	8	Constipation	Drugs for urinary frequency, enuresis and incontinence, Opioid analgesics, NSAIDs, Cytotoxics, Calcium channel blockers, Calcium supplements, Drugs used in nausea	No prophylaxis given
Possibly	6	Diarrhoea	Antibacterial	Query appropriate indication, signs/symptoms of viral illness
Possibly	1	Gastritis	Corticosteroids	Past history of gastritis- could have given appropriate prophylaxis?
Possibly	2	Haematemesis	NSAIDs	Developed haematemesis with vomiting. Avoidable with improved education
Possibly	1	Hyperglycaemia	Corticosteroids	Prolonged course of steroids/monitoring frequency
Possibly	6	Hypoglycaemia	Drugs used in diabetes	Avoidable with improved patient education – for example insulin use when unwell. Frequency of monitoring

Possibly	1	Ileus	Opioid analgesics	Avoidable with more rational prescribing- lots of opioids were given
Possibly	2	Immunosuppression	Corticosteroids, Drugs affecting the immune response	Frequency of monitoring of drug levels. More rational prescribing
Possibly	1	Rash, lip swelling	Anti-bacterial	History of the same ADR to the same medicine
Possibly	6	Respiratory depression	Drugs used in status epilepticus, Hypnotics	Alternative medicine available. Multiple doses given. Dose slightly high and multiple doses given
Possibly	1	Seizure	Antihistamines	History of seizure in the past with similar antihistamine
Possibly	1	Vomiting	Anti-bacterial	Appropriate indication for antibiotics signs/symptoms of viral illness?
Possibly	1	Hyperglycaemia	Parenteral preparations	Frequency of monitoring

Table 5.3 shows the possibly and definitely ADR cases, the drug classes involved in the ADR and a rationale for avoidability. Table 5.4 shows the avoidability themes associated with ADRs categorised as either possibly or definitely avoidable. Table 5.5 shows the results from the validation check where MT checked 10% of the cases.

Table 5.4 Avoidability themes associated with ADRs

Avoidability theme	Number of possibly avoidable cases	Number of definitely avoidable cases	Proportion of ADRs associated with each theme for avoidable ADRs	Proportion of ADRs associated with each theme for all ADRs	Therapeutic areas involved in this theme (number for each area)
Inappropriate or suboptimal prescribing	26	4	60%	12%	Opioid analgesics (4) Drugs used in nausea (3) Cytotoxics (3) Antibacterial (8) Corticosteroids (2) Antihistamines (1) Drugs used in status epilepticus (6) Hypnotics (1) Drugs for urinary frequency, enuresis and incontinence (1) Antiepileptics (1) Muscle relaxants (1) Topical corticosteroids (1) Calcium channel blockers (1) Calcium Supplements (1)
Inadequate monitoring	10*	3	25%	5%	Drugs affecting the renin-angiotensin system (1) Corticosteroids (4) Drugs affecting the immune response (1) Opioid analgesics (1) Drugs used in diabetes (5) Parenteral preparation (1)
Inadequate education	6*	1	15%	3%	Drugs used in diabetes (3) Anti-motility drugs (1) NSAIDs (2)
*Two possibly avoidable ADRs were categorised in two themes (inadequate monitoring and inadequate education)					
	Number	Proportion of eligible admissions (8345) taken from Gallagher et al. 2012			
All avoidable ADRs	48	0.6%			

Table 5.5 Results from validation -10% check

ADRID	ADR Type	LAAT Outcome MT	LAAT Outcome LB	Hallas Outcome
2	Seizure	Not avoidable	Not avoidable	Possibly avoidable
6	Neutropenia	Not avoidable	Not avoidable	Possibly avoidable
19	Rash, lip swelling	Possibly avoidable	Possibly avoidable	Definitely avoidable
60	Hypoglycaemia	Not avoidable	Not avoidable	Possibly avoidable
227	Hypercalcaemia	Not avoidable	Not avoidable	Possibly avoidable
235	Adrenal suppression	Possibly avoidable	Possibly avoidable	Definitely avoidable
9	Immunosuppression	Not avoidable	Not avoidable	Not avoidable
13	Diarrhoea	Not avoidable	Not avoidable	Not avoidable
17	Constipation	Possibly avoidable	Possibly avoidable	Possibly avoidable
32	Deranged LFTs	Not avoidable	Not avoidable	Not avoidable
33	Epigastric pain	Not avoidable	Not avoidable	Not avoidable
64	Nausea	Not avoidable	Not avoidable	Not avoidable
81	Mucositis	Not avoidable	Not avoidable	Not avoidable
83	Hyperkalemia	Not avoidable	Not avoidable	Not avoidable
119	Headache	Not avoidable	Not avoidable	Not avoidable
122	Vomiting	Not avoidable	Not avoidable	Not avoidable
146	Post-tonsillectomy bleed	Not avoidable	Not avoidable	Not avoidable
160	Increased appetite	Not avoidable	Not avoidable	Not avoidable
164	Ileus	Not avoidable	Possibly avoidable	Possibly avoidable
167	Deranged Renal Function	Not avoidable	Definitely avoidable	Definitely avoidable
187	Haematemesis	Not avoidable	Possibly avoidable	Possibly avoidable
228	Gastritis	Definitely avoidable	Possibly avoidable	Possibly avoidable
79	Hyperglycaemia	Not avoidable	Possibly avoidable	Possibly avoidable
1	Respiratory depression	Not avoidable	Possibly avoidable	Possibly avoidable
4	Intestinal obstruction	Not avoidable	Possibly avoidable	Definitely avoidable

5.4.1 Results from the validation check

The results from the validation check are summarised in Table 5.5. Overall %EA agreement was 72%. Of the seven case reports where disagreement occurred, 6/7 had the same avoidability classification assigned by LB using the LAAT as those determined using the Hallas scale.

***Please note some of the identifiable data has been removed from the ADR case reports in order to protect patient confidentiality. ***

The cases with disagreement are described below.

ADRID 164 - Ileus

A surgical patient with Spina Bifida and neuropathic bladder who was readmitted the day after discharge (six days after bladder surgery) with vomiting and abdominal pain was diagnosed with ileus. Suspected medicines were codeine and fentanyl. Post operatively whilst in hospital the patient had a fentanyl patient controlled analgesia (PCA) for 3 days and received regular codeine. They did not open their bowels until day 4 post-op. On day 5 post-op the patient required a glycerine suppository which was reported to be ineffective they were later discharged home and mum said they had lactulose at home. The patient was readmitted the next day due to vomiting (unable to keep fluids down) and they complained of intermittent abdominal pain which was reported to be relieved by vomiting. Prior to admission they passed a small hard bowel motion that morning at home. On exam their abdomen was reported to be soft, distended and no bowel sounds present. An abdominal x-ray showed dilated upper loops. A nasogastric tube (NG) was passed. They were treated with lactulose, a phosphate enema and IV fluids. The patient reportedly had a faecal vomit overnight and the following night opened their bowels. The next day they tolerated fluids and started light diet. The patient was discharged home three days later.

The Hallas assessment for this case was 'possibly avoidable' and the reason provided was "ileus after 6 days post-op opioid use, avoidable with more rational prescribing (possibly use alternative analgesia).

In terms of the avoidability assessments using the LAAT one reviewer categorised the case as 'possibly avoidable' and the other as 'not avoidable'. Divergence occurred answering the question 'Were there known preventative strategies and/or appropriate management plan(s), with information about the ADR and its avoidance, available?' One reviewer answered 'yes' here which took them on to answer 'Were other information sources, or information in the history available for prevention of the ADR which could have been followed?' they answered 'yes' here and went on to categorise the ADR as 'possibly avoidable' (the rationale provided was that the patient was given a lot of opioids). The other reviewer answered 'no' to the question 'Were there known preventative strategies and/or appropriate management plan(s), with information about the ADR and its avoidance, available?' They answered 'no' to the question 'Were other information sources, or information in the history available for prevention of the ADR which could have been followed?' which led to them categorising the case as 'not avoidable'. The rationale provided was that the opioids were presumably deemed necessary to control the pain and other options for pain relief had been considered by the clinical team.

ADRID 167- Deranged renal function

A baby with heart disease had deranged renal function (raised urea and creatinine on admission to Alder Hey) following treatment with captopril at another hospital. Prior to commencing captopril at the other hospital the patient's urea (UR) and creatinine (CR) were raised (UR 14.8 mmol/l and CR 73 micromol/L) (normal values for age range: UR 2.0-5.0 mmol/l and CR < 40 micromol/L). Three days after commencing captopril the patient's UR had increased to 25.5 mmol/l and their CR had increased to 101 micromol/L. The captopril was stopped on admission to Alder

Hey as it was suspected as causing the renal dysfunction. The urea and electrolytes (U+Es) were reported to have improved upon stopping the captopril. Two days after stopping the captopril the patient's UR had decreased to 15.9 mmol/l and their CR had dropped to 55 micromol/L. The medical team considered restarting the captopril later once the U+Es had improved but this wasn't done. Monitoring of U+Es was completed but the frequency was variable between 3 and 6 days.

The Hallas assessment for this case was 'definitely avoidable' and the reason provided was "avoidable with improved monitoring". In terms of the LAAT avoidability assessments there was extreme disagreement for this case, one reviewer categorised it as 'definitely avoidable' and the other reviewer as 'not avoidable'. Both reviewers answered 'yes' to the question 'Were there known preventative strategies and/or appropriate management plan(s), with information about the ADR and its avoidance, available?' which led them to answer the next question 'were the strategies and/or management plan(s) followed? One reviewer answered 'no' here and categorised the ADR as 'definitely avoidable' the rationale provided was the frequency of the monitoring particularly in a child who had deranged renal function prior to initiating the captopril. The other reviewer answered 'yes' therefore categorising the ADR as 'not avoidable'. The rationale provided was that the initial baseline renal dysfunction could not have been avoided but perhaps the extent of the exacerbation of renal dysfunction could have been minimised. If starting captopril was clinically appropriate then the only way to detect worsening renal function would be to monitor renal function but by the time worsening renal function was detected then it would have already have happened. Thus worsening renal function could not have been avoided by more frequent monitoring. Discussion of this case between the two reviewers highlighted the subtleties in interpretation of the questions and information contained in the case reports. The reviewer who assessed the ADR as unavoidable was working to assess the occurrence of the ADR while other reviewers may have had a different perspective.

ADRID 187- Haematemesis

A child under 6 years with a 2 days history of vomiting was reported to have been vomiting every hour. They were given a dose of paracetamol and ibuprofen. Was reported to have had haematemesis the following morning, at first coffee ground vomit followed by 5 bright red fresh blood vomits. Admitted for observation later discharged as haematemesis had stopped and the patient was tolerating diet and fluids.

The Hallas assessment for this case was 'possibly avoidable' and the rationale provided was "avoidable with improved patient education/more rational prescribing (less NSAID use)". Using the LAAT one reviewer classified the case as 'possibly avoidable' the rationale provided was 'perhaps ibuprofen was not appropriate as the patient was vomiting regularly and not able to tolerate food one of the counselling points with ibuprofen (as per BNFC guidance) is to be taken with or just after food. This ADR might be 'possibly avoidable' with improved education.' The other reviewer categorised the ADR as 'not avoidable' by answering 'no' to 'Were there known preventative strategies and/or appropriate management plan(s), with information about the ADR and its avoidance, available?' which led them to the next question 'Were other information sources, or information in the history available for prevention of the ADR which could have been followed?' answering 'no' here took the reviewer to 'not avoidable'. The reviewer felt that the family had acted within standard practice for families and that improved education that would reach every family about every warning relating to commonly used children's medicines was a theoretical possibility with minimal relevance in the real world. Answering 'yes' to 'Were there known preventative strategies and/or appropriate management plan(s), with information about the ADR and its avoidance, available?' took the other reviewer to 'Was appropriate action taken to avoid the ADR'. They answered 'no' here and therefore categorised the ADR as 'possibly avoidable'. The divergence here appeared to relate to the extent to which

all theoretical possibilities were considered relevant to the assessment and the extent to which the assessment should be guided by “real world” thinking.

ADRID 228 - Gastritis

This gastritis case occurred in an oncology patient who was prescribed dexamethasone as part of their treatment regime for acute lymphoblastic leukaemia (ALL). It was recorded in the case history that they had experienced gastritis during a previous admission which was initially treated with Gaviscon Advance® prn, before ranitidine was added in twice daily the patient appeared to subsequently be switched to omeprazole once daily but it was not clear why, there was no mention of how effective the treatment was or when it resolved. On this occasion the ADR was detected after the patient complained of left sided chest pain and was admitted for observation. A diagnosis of gastritis secondary to steroids was made. The ranitidine was restarted which was reported to be effective and the symptoms resolved. No further reports of gastritis were reported although the case report stated that the steroid course was completed shortly after the admission. In terms of the avoidability assessments using the LAAT one reviewer categorised the case as ‘possibly avoidable’ and the other as ‘definitely avoidable’ this was due to the differences in answering the question ‘Were there known preventative strategies and/or appropriate management plan(s), with information about the ADR and its avoidance, available?’ Answering ‘no’ to this question (as prophylactic ranitidine or other gastro-protective treatment is not listed in the ALL treatment protocol) takes the reviewer on to ‘Were other information sources, or information in the history available for prevention of the ADR which could have been followed?’ answering ‘yes’ to this question (based on the fact that we know the patient had a history of gastritis on a previous admission and required treatment) takes the reviewer on to answer ‘was appropriate action taken to avoid the ADR?’ and answering ‘no’ to this categorises the ADR as ‘possibly avoidable’. The other reviewer answered ‘yes’ to the question ‘Were there known preventative strategies and/or appropriate management plan(s), with information about the ADR and its

avoidance, available?’ which led them on to answer ‘were the strategies and/or management plan(s) followed?’ and in answering ‘no’ here categorised the ADR as ‘definitely avoidable’.

In theory, perhaps ranitidine could have become part of the personalised management plan for this child however this would have meant a change in the tool’s glossary to incorporate ‘personalised management plan’ in the section where other management plans are listed. At the time of assessment we defined appropriate management plans as per the statement below (See glossary in appendix):

Appropriate management plan(s): a plan that would be recognised as appropriate by a reasonable body of opinion. This could refer to **any** local, national or international guideline that could be available to the prescriber e.g. hospital guidelines, National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN). The glossary was subsequently amended to reflect this change (see Appendix 8 for the final version of the glossary):

Appropriate management plan(s): a plan that would be recognised as appropriate by a reasonable body of opinion. This could refer to **any** local, national or international guideline that could be available to the prescriber e.g. hospital guidelines, National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN) or a ‘personalised management plan’.

ADRID 79 - Hyperglycaemia

The hyperglycaemia case occurred in a child under 12 with ulcerative colitis gastric symptoms who had been on oral prednisolone 30-40mg for 3-4 months. It was reported that they had tried several times to reduce the dose but after symptoms worsened the dose was increased again. The patient reported an increased frequency of passing urine at home (up to 30 times/day). They presented to accident and emergency (A&E) with glycosuria and a blood sugar of 14.7. Seen by

endocrine team who thought it was ADR to prednisolone and prescribed insulin to control symptoms.

The Hallas assessment for this case was 'possibly avoidable' and the rationale provided was 'avoidable with more rational prescribing (prolonged course of steroids used)'. Using the LAAT one of the reviewers categorised the ADR as 'possibly avoidable' and the other as 'not avoidable'. The divergence occurred at the question 'Was appropriate action taken to avoid the ADR?'; one reviewer answered 'no' here categorising the ADR as 'possibly avoidable' the rationale provided was guidance from the BNFC suggests using the lowest possible dose (treatment might be required for 4-8 weeks), frequent monitoring and dose reduction perhaps the dose could have been tapered sooner? The other reviewer answered 'yes' categorising the ADR as 'not avoidable': making the assumption that the treating team had made all reasonable effort to reduce the dose – once reduction had been tried "several times" it would be unreasonable to subject the child to unnecessary flareups since not every child would develop diabetes on steroids while this child would develop flareups. The divergence in this case appeared to the balance between different assessments of causal chains that clinicians make in practice.

ADRID 1- Respiratory depression

The respiratory depression occurred in a child with epilepsy who was started on desmopressin 5 days prior to the seizure. Had status epilepticus and was given diazepam rectally in school. Decreased respiratory effort and decreased Glasgow Coma Scale (GCS) patient was unresponsive. They required intubation and ventilation and were admitted to PICU. They recovered on PICU and no further problems were reported.

The Hallas assessment for this case was 'possibly avoidable' and the rationale provided was 'alternative medicine available, avoidable with more rational

prescribing'. Using the LAAT one reviewer categorised the ADR as 'possibly avoidable' and the other as 'not avoidable'. The divergence occurred at the question 'Were other information sources, or information in the history available for prevention of the ADR which could have been followed?' One reviewer answered 'yes' categorising the ADR as 'possibly avoidable' and the other reviewer answered 'no' categorising the ADR as 'not avoidable'. The rationale provided for categorising the ADR as 'possibly avoidable' was alternative medicines were available. The other reviewer assumed if the medicines had been available to the team treating the child they would have been used. In this view, if the treating team had no choice about the medicine then the ADR was not avoidable. The way to avoid the ADR would be for the health care system (school, ambulance, neurologist etc.) to make a different policy decision. This view led to a discussion of proximate and distal (ultimate) causes. According to the WHO 'the chain of events leading to an adverse health outcome includes both proximal and distal causes' (World Health Organisation 2002). The proximate cause of ADRID 1 was the use of diazepam. The ultimate cause was the selection of medicines outside the hospital setting. One reviewer examined the proximate cause of the ADR. The other reviewer examined the distal cause of the ADR. Assessors could set different limits on the search for distal causes and this might lead to different assessments of avoidability.

ADRID 4- Intestinal obstruction

The patient had a history of diarrhoea and abdominal pain for 4 days. They were prescribed loperamide. The day before admission they were reported to have not opened their bowels for 2 days. They reported worsening abdominal pain so the loperamide was stopped (after 4 days of treatment). On admission they had a contrast study which showed obstruction. They went to theatre and had adhesiolysis, resection of small gut and reanastomosis. The pathology report showed gangrenous small gut section with impacted faeces.

The Hallas assessment for this case was 'definitely avoidable' and the rationale provided was 'could be prevented by improved patient/parent education'. In terms of the LAAT assessments one reviewer categorised the ADR as 'possibly avoidable' and the other as 'not avoidable'. The divergence occurred at the question 'Was appropriate action taken to avoid the ADR?' one reviewer answered 'no' categorising the ADR as 'possibly avoidable' and the other reviewer categorised the ADR as 'not avoidable'. The rationale provided for assessing the case as 'possibly avoidable' was that it was potentially avoidable with improved patient/parent education. The parents should have been counselled on what to look out for and when to stop the medicine. The patient information leaflet states that loperamide can be taken for up to 5 days but if no improvement after 2 days of taking the first dose of loperamide to go back and visit the doctor. The rationale for the response "not avoidable" was that intestinal obstruction was due to the adhesions which were not due to loperamide.

Some of the divergence is related to the burden of proof required for avoidability. One position is that avoidability relates to any conceivable different course of action. Another position is that avoidability relates to plausible courses of action. If these positions are widely held then some degree of divergence may be unavoidable, particularly within the group of people working to "plausible" courses of action. The sources of divergence may reflect personality type, approach to clinical care or practical experience. The divergence is analogous to the burden of proof in civil cases "balance of probability" vs "beyond a reasonable doubt". For example the evaluation of clinical features may be done in more than one way. One extreme would be to consider clinical features to be relevant if they contributed to the ADR beyond a reasonable doubt. Another approach would be to consider clinical features to be relevant if they contribute on a balance of probabilities.

Personal reflection on different approaches to using the LAAT

During the development and validation of the LAAT I observed many different people from different backgrounds and professions with varying levels of experience use the LAAT. I observed different approaches to assessing the avoidability of ADR case reports with some clinicians taking a very practical approach and others a more theoretical approach where they considered many aspects of avoidability and made comments that the ADR may not be avoidable on this occasion but would be avoidable on any subsequent occasions. Some took a systematic approach and were careful to answer the questions in the same way when assessing different cases of the same ADR types. Others were less consistent and at times showed evidence of interpreting the questions differently for different cases of the same ADR type, perhaps sometimes this was due to subtle differences in the case reports but not always. Some reviewers appeared to have a predefined opinion on whether or not the case was avoidable before conducting an avoidability assessment with the LAAT and then went on to answer questions in a certain way in essence using the tool as a validation check to confirm their line of thinking.

5.5 Discussion

The LAAT showed good agreement overall with Hallas (1990), good agreement for the non-oncology cases and moderate agreement for the oncology cases. The sub-categorisation of the analysis into oncology and non-oncology cases showed a marked change in the number of avoidable cases. Overall assessment with the LAAT showed that approximately 19% of cases were either possibly or definitely avoidable. This figure increased to almost 32% for the non-oncology cases and decreased to 5.8% for the oncology cases. This was comparable to the Hallas assessments where overall avoidability was approximately 22%; this increased to approximately 37% for the non-oncology cases and decreased to approximately 7% for the oncology cases (Gallagher et al. 2012).

The reason for this marked difference may be explained by the nature of the oncology ADRs. Of the 120 oncology cases, the most common reactions were neutropenia (89), thrombocytopenia (55) and anaemia (38) (Gallagher et al. 2012). These ADRs are expected, largely 'not avoidable' given the benefit risk ratio and accounted for over 40% of all oncology ADRs⁴. Although some possible prevention strategies for neutropenia are used in adults such as granulocyte colony stimulating factors (GCSF) there is no definite evidence regarding the use of GCSF in children (Sasse EC et al. 2005). This may explain the drop in the number of avoidable ADRs from 19% overall to 5.8% for the oncology ADRs. The types of oncology ADRs which were classified as possibly or definitely avoidable were constipation without laxative prophylaxis, vomiting after chemotherapy where additional antiemetic prophylaxis could have been given and gastritis following the use of corticosteroids in a patient with a past history of gastritis following corticosteroid use. The gastritis case might have been avoidable if the patient was given appropriate prophylaxis such as ranitidine.

The systematic review by Smyth et al. (2012) highlighted two key points regarding avoidability. Firstly, they found a noticeable lack of avoidability data; with only 19% of studies assessing avoidability. Data were available for fourteen studies and the avoidability rates differed greatly amongst studies; with 7-98% of ADRs categorised as possibly/definitely avoidable. One of the possible reasons for the wide variation may be explained by the difference in study types, which included those causing admission, in hospital, community and combined settings (causing admission and in hospital). Another possible reason is the method used for assessing avoidability; ten studies used a recognised avoidability assessment tool. Half of the studies used Schumock and Thornton (1992) and Hallas (1990) was also used.

The assessment of the ADRIC admissions study cases did highlight a discrepancy on two separate occasions. Firstly, the ADR of rash and lip swelling due to amoxicillin in

⁴ 431 reactions in 249 ADR case reports

a patient with a history of the same ADR previously to amoxicillin; assessment of this case using the LAAT categorised the ADR as 'possibly avoidable'. Although the reviewer wanted to categorise it as 'definitely avoidable' the tool didn't allow this as a route. The route taken was via the central boxes 'Was there a known history of allergy or previous similar reaction to the drug' - answered 'yes' which led to 'Were other information sources, or information in the history available for prevention of the ADR which could have been followed' - answered yes (patient had a history of same ADR), 'Was appropriate action taken to avoid the ADR?' - answered 'no' and therefore the ADR was classified as 'possibly avoidable'. The Hallas assessment for this case was 'definitely avoidable' with the rationale provided as 'same ADR previously to same medication' (Gallagher et al. 2012). The second case was a gastritis case where the ADR was due to dexamethasone; the patient had a history of gastritis since commencing steroids and had been prescribed ranitidine in the past for this. However, there was no information available in the case report on the efficacy of the ranitidine during the previous episode of gastritis. Assessment of this case using the LAAT categorised the case as 'possibly avoidable' based on the patient having a history and appropriate action not taken to avoid the ADR. The Hallas assessment of this case was 'possibly avoidable' with the rationale provided as 'previous gastritis - possibly avoidable with improved prophylaxis'. This case was also assessed by MT as part of the 10% validation and categorised as 'definitely avoidable'. It highlighted the need for an amendment to the tool's glossary to include 'personalised management plan' under appropriate management plans (see Appendix 8 for details) to allow for this in future assessments.

As discussed earlier the divergences relate to the burden of proof required for avoidability. The assessment of avoidability is complex and subjective which may lead to a degree of divergence which is unavoidable. The LAAT aims to minimise the subjectivity by taking the reviewer through a series of questions however, it is impossible to eliminate subjectivity completely as reviewers may differ in their beliefs, experience and approach. This was evident in the qualitative work discussed

in Chapter 4, there were elements of bounded rationality and heuristics displayed in the ADR assessments by the consensus groups. See Chapter 4 for a discussion of heuristics.

Thus, as noted at the end of Chapter 3, implementing an AAT will require more than developing a tool, validating it and rolling out. It will be important to identify systematic differences between people and groups. These differences may be mitigated through training or interpretation. Training could point out the differences and ask assessors to take a specific approach in the interests of consistency. Interpretation could take account of the variation that is intrinsic to the process of avoidability assessment (see Chapter 6).

One of the objectives of this thesis was to identify potentially avoidable ADRs and investigate ways to reduce their incidence. In terms of avoidability constipation was the ADR most frequently categorised as avoidable with nine cases in total classified as either 'definitely' or 'possibly avoidable'. The reason for these cases being potentially avoidable was that no laxatives were given prophylactically. Eight out of the nine constipation cases assessed with the LAAT were classified as 'possibly avoidable' rather than 'definitely avoidable' as there is not always a guideline available. Other examples of potentially avoidable ADRs include immunosuppression, respiratory depression, vomiting and hypoglycaemia. Three key themes for avoidability have been established through a review of the existing literature (Jonville-Béra et al. 2009, Smyth et al. 2012, Gallagher et al. 2012, Temple et al. 2004) the themes are:

1. Inappropriate or suboptimal prescribing - this includes failure to follow written recommendations or failure to apply information derived from other sources. Specific examples include:
 - Inappropriate indication: diarrhoea due to antibiotics prescribed for a viral infection

- Inappropriate duration of treatment: adrenal suppression due to 2 years' continuous treatment with intranasal corticosteroid
 - Medication administered to patient with history of ADR: seizure due to antihistamine use in a patient who had previously experienced the same reaction to the same medication
 - Preventative measures not implemented: laxatives not prescribed and patient developed constipation due to opioid use
2. Inadequate monitoring again this includes failure to follow written recommendations or failure to apply information derived from other sources, for example:
- Hypercalcaemia in a patient receiving oral calcium supplementation
3. Inadequate patient or parent education, for example:
- Hypoglycaemia due to failure to adjust insulin dose when child unwell at home
 - Prolonged diarrhoea due to continuation of laxatives when diarrhoea first developed

There was evidence of these themes in the assessment of the ADR cases in this study, as summarised in Table 5.4. The next step is to develop strategies to prevent these types of ADRs. This will be discussed in Chapter 6. This work also provides a preliminary estimate of the frequency of the incidence of the three avoidability themes. Table 5.4 avoidability themes associated with ADRs suggests that the inappropriate or suboptimal prescribing theme is the most frequent and this could be one way to prioritise educational interventions. With respect to therapeutic areas antibacterials were the most frequently implicated drug class involved in avoidable ADRs and this could be another way to target efforts. The overall incidence of avoidable ADRs was 6 per thousand admissions (Table 5.4). This figure is based on ADRs causing admission, although it was not possible in this study to

look at the incidence of avoidable ADRs in inpatients, preliminary findings based on work in Chapter 2 suggest that the figure would look quite different for inpatient ADRs due to the difference in nature and types of ADRs. This estimate is likely to be an underestimate because some ADRs are not detected on admission.

The development of the LAAT was an iterative process conducted by a MDT using ADR case reports from the ADRIC study. We have conducted extensive testing of the LAAT including both individual and group testing. In addition to this rigorous testing, we have followed the recommendations set out in a recent systematic review of methods for assessing avoidability (Hakkarainen et al. 2012a).

A limitation of this study was that LB only assessed the cases using only the LAAT and not Hallas in addition to allow a direct comparison. Secondly, LB assessed the cases individually whilst the Hallas assessments were conducted in a group. Although the decision to conduct the assessments individually was taken after the consensus meeting and individual testing phase which showed that there was no real difference between individuals or groups using the LAAT (Chapter 3). Due to feasibility of assessments it was decided that the ADR cases would be assessed individually. The good agreement in this study between Hallas and the LAAT has shown that individual avoidability assessments are possible using the LAAT. It has also shown that the Hallas scale (1990) is a suitable alternative tool to use depending on the study population, as we know from the ADRIC inpatient study there were difficulties using Hallas due to the language used, the breadth of knowledge required and the conditions represented in the cohort (Thiesen et al. 2013).

The LAAT removes some of the subjectivity that perhaps makes it easier for less experienced assessors to use the tool. The questions on the tool are designed to guide the reviewer through a particular pathway to one of the four avoidability categories. Hallas may be quick and easy to use by experienced assessors but can be difficult to use by those with less experience of assessing avoidability, in which

instance it may work best as a consensus group. The LAAT assesses whether at the time the drugs were prescribed and administered if the ADR was avoidable or not. This is where the LAAT differs to Hallas, in that Hallas really is about reflecting on whether you have read some obscure or new paper somewhere that you ought to be applying in practice. This is one of our reasons for not using Hallas in the inpatient study as it seemed to us not to be appropriate in terms of talking about avoidability at the time. This study has shown very similar results for the two tools, however, one tool was used in a consensus group setting (Hallas scale) and the other (LAAT) by an individual assessor. Therefore, depending on the study team, study population, time constraints and personal preference then either tool may be suitable for assessing avoidability of ADRs.

The LAAT did not give consistent results for a number of reasons. Some of the reasons for this were explained earlier in this chapter in the section on personal reflection on the different approaches to using the LAAT. Firstly, assessors applied the LAAT in different ways. This occurred for a number of reasons. Some, but not all assessors were inconsistent. Assessors have different approaches to establishing the nature of expected management for a clinical case. Some assessors expected to review guidelines for every case; others were prepared to base their judgments on recall of guidelines that could be incomplete or inaccurate. Other assessors did not consult guidelines at all. These findings suggest that consistent assessment of avoidability requires more than the introduction of a structured assessments tool. Secondly, many guidelines did not include information about ADRs and ways to prevent ADRs. This allowed assessors to take a number of approaches to assessment (as well as being a primary way to reduce avoidable ADRs).

Thirdly, assessors bring different cognitive styles to the assessments. This was illustrated by the comparisons between LB and MT. Discordant assessments could arise because of different standards of proof. Did an ADR have to be not avoidable beyond a reasonable doubt, or could an ADR be not avoidable on a balance of

probabilities? How far down the chain of causality should one search before concluding that none of the causal links contributed to avoidability? How much variation in practice between clinicians and families is appropriate when handling complex balances between benefit and the risk of avoidable ADRs? These three reasons for inconsistency suggest that there will always be an irreducible lack of consistency during the assessment of whether ADRs are avoidable. The implications of this are discussed further in Chapter 6.

5.6 Conclusion

In summary, we have designed a new avoidability assessment tool, developed by a multidisciplinary team that had good agreement with the existing Hallas (1990) assessments that were carried out as a group consensus. This chapter has shown that individuals can use the new tool effectively. This is an advantage as the time constraints and organisational issues involved in holding MDT consensus meetings can be challenging at times. This study found the incidence of avoidable ADRs to be 19.3% which was similar to that found by Gallagher et al. (2012) using the Hallas scale (1990). However, we know from the recent systematic review (Smyth et al. 2012) that avoidability rates varied widely between studies; with 7-98% of ADRs being classified as possibly/definitely avoidable. This work has also provided a preliminary estimate that 6 per 1000 admissions to a children's hospital are due to avoidable ADRs. Further work needs to be conducted in this area to determine the avoidability rate of ADRs in children and identify the potentially avoidable ADRs in order to develop possible prevention strategies. Unfortunately, it was outside the scope of this thesis but plans for future work include the avoidability assessment of all the ADRIC inpatient study cases. This would enable us to focus on the potentially avoidable ADRs and ideally develop prevention strategies to reduce the incidence of ADRs in children. A more in-depth, expert-led review of avoidable ADRs and their prevention is required before detailed and clinically relevant interventions can be implemented.

Chapter 6: Discussion

6.1 Thesis findings - Summary

This thesis focuses on the assessment of the avoidability of adverse drug reactions in children. The impetus leading to the work was the lack of information about the avoidability of ADRs in children. The ADRIC systematic review highlighted that very few studies investigated avoidability (19%) and, when they did, there was wide variation in the avoidability rates between the studies (7-98%) (Smyth et al. 2012). Secondly, difficulties were encountered during the assessment of avoidability in the ADRIC inpatient study using existing tools (Thiesen et al. 2013).

The overall aim of this thesis was to develop a new avoidability assessment tool suitable for use in paediatrics (Chapter 2) as none of the existing tools were specifically designed for use in children. This thesis also looked at the methodology for assessing ADR avoidability and compared individuals to group assessments (Chapters 3 and 4). In Chapter 3 the hypothesis that group avoidability assessments were superior to individual avoidability assessments was tested. Chapter 4 examined the qualitative aspects of decision making in MDTs. Finally, in Chapter 5 the newly developed LAAT was used to assess the avoidability of the cases from the ADRIC admissions study and compared to the results of the existing assessments using the Hallas method from the ADRIC programme (Gallagher et al. 2012, Hallas et al. 1990). This thesis aimed to establish which types of ADRs are avoidable and to describe the context of avoidability of ADRs in the care of children. It also aimed to identify potential strategies for clinical practice that might reduce the incidence of ADRs.

There is large variation in the reported avoidability rates of ADRs in paediatrics; work from this thesis suggests that approximately 20% of ADRs involved in causing admission to hospital are avoidable (Chapter 5). This is similar to the assessments

made by Gallagher et al. (2012). In adults this figure is higher; a meta-analysis conducted by Hakkarainen et al. (2012b) found that roughly half of all ADRs amongst adult inpatients (45%) and outpatients (52%) may be avoidable. Assessing the avoidability of ADRs is a complex process which requires consideration of a number of factors. There are different levels of avoidability including patient, ward, departmental, institutional, professional and national.

Despite these complexities a number of previous studies have been conducted. This experience prompted the assumption that it would be relatively straightforward to develop a new scale using the methodological suggestions put forward by Hakkarainen (2012a). However, we found several difficulties with avoidability that have not previously been described in the literature. A common theme that emerged in the work undertaken in Chapters 3 and 4 of this thesis was the lack of available treatment guidelines. Where guidelines were available few contained information about ADRs or preventative strategies. The majority of clinicians relied on their experience and tacit knowledge rather than on guidelines.

In adults, ADRs contribute significantly to patient morbidity, mortality and hospitalisation costs (Davies et al., 2009, Khan 2013). The impact of ADRs in paediatrics is not as well quantified (Khan 2013); however, it is expected to include similar types of costs. These costs include additional clinician time, additional diagnostic tests, treatment and prolonged hospitalisation (Visconti and Smith 2006). Therefore, work to quantify the impact of ADRs in children and the development of interventions to reduce that impact are important.

In the ADRIC admissions study, 129 ADRs were detected in non-oncology patients. 36.4% of these were possibly or definitely avoidable (Gallagher et al., 2012). If some of the ADRs detected were avoidable, this implies that the right intervention at the right time would have prevented the ADR. A thorough exploration of avoidable ADR cases is needed to inform the development of practical interventions that can be

translated into clinical practice. This work was beyond the scope of this thesis but is a logical development of the work completed to date. In Chapter 5, three main avoidability themes were described with inappropriate or suboptimal prescribing being the most common theme. Inappropriate or suboptimal prescribing accounted for 60% of the ADRs categorised as either possibly or definitely avoidable. Raising awareness of ADRs with prescribers and incorporating training in teaching sessions at undergraduate and postgraduate levels may help to reduce the number of ADRs. This is discussed in more detail in Section 6.3.1 Identification of potentially avoidable ADRs and strategies to reduce their incidence.

6.2 Interpretation of findings and limitations

6.2.1 Development of a new avoidability assessment tool

The aim of this study was to develop a new avoidability assessment tool that was suitable for use in specialist in-patient paediatrics, was generalisable to other settings where the abstract concepts included in the Hallas score are impracticable and met all the criteria of a good tool as described by Hakkarainen et al. (2012a). No tools were available specifically for characterisation of ADRs in children and therefore there was a requirement to develop such tools (Smyth et al. 2012). The development of the LAAT was an attempt to improve the assessment of avoidability of ADRs in children in paediatric inpatients across all subspecialties of paediatrics. Multiple testing phases were conducted. A limitation of this study was the number of cases assessed in the different phases with twenty cases being used for some of the assessments. This was due to feasibility and time constraints. This resulted in the development of a new avoidability assessment tool by a MDT, which we believe to be at least equivalent to, if not more appropriate for use in paediatrics than, the Hallas scale. The LAAT is practicable and has undergone extensive testing and validation. The new tool was used effectively by individuals and by groups. Use by

individuals is an advantage as the time constraints and organisational issues involved in holding MDT consensus meetings can be challenging at times.

6.2.2 Consensus meetings, individual testing and qualitative work

Chapters 3 and 4 of this thesis investigated if group assessments were superior to individual avoidability assessments and explored factors that influenced decision-making in MDT consensus meetings. A mixed methods approach was taken. Quantitative analysis examined the extent to which individuals and groups agreed with the 'gold standard' as outlined in Chapter 3 and qualitative methods were chosen to gain an insight into clinician's thoughts, experiences and practices in relation to the assessment of ADR avoidability, Chapter 4.

Following initial testing of the LAAT with individuals it was decided to investigate if group avoidability assessments were superior to individual avoidability assessments. It was hypothesised that MDT groups would be superior to individual assessments given the nature of the assessments. However, agreement with the 'gold standard' was similar for individuals and groups. In terms of %EA individuals had marginally better agreement with the 'gold standard' than the consensus groups. The cases were informative with marked divergences for some ADR types. Possible reasons for divergence might be evidence based, practice based or irreducible divergence. The small sample size was a limitation of the study and therefore caution should be taken with over interpretation of the data; but the divergences show what is possible within overall performance. The LAAT supports consistency within a single assessor or group and has face validity for paediatrics.

Clinicians were generally positive about using the tool but there was some confusion about concepts and terminology that may need addressing. They seemed to rely more on tacit knowledge and experience (either their own or others) than on guidelines although, the consensus groups consulted more guidelines than the

individuals (or at least those individuals that specified if guidelines were consulted). The consensus groups were more inclined to attribute a 'definitely' or 'possibly' avoidable assessment to the cases than the individuals. For some cases there was complete agreement between the three consensus groups but disagreement with the 'gold standard'. The groups developed specific heuristics based on the personal preferences and group behaviour.

6.2.3 Comparison to existing tools

One of the recommendations by Hakkarainen et al. (2012a) was to compare newly developed assessment tools to existing ones so that if one or more tools(s) gained rigorous evidence and became a gold standard it would facilitate the comparison of different studies. We compared the LAAT to Hallas (1990) for the assessment of the ADRIC admissions study ADR cases (Gallagher et al. 2012).

A limitation of this study was that the individual assessment of the cases was done using only the LAAT, and not Hallas as well to allow a direct comparison. Secondly, the LAAT assessments were conducted by an individual and compared to Hallas assessments which were conducted in a group setting. Although the decision to conduct the assessments individually was taken after analysis of the work conducted in Chapter 3; which showed that there was no real difference between individuals or consensus groups in terms of agreement with the 'gold standard'. Therefore, from a practical standpoint it was decided that the cases would be assessed individually. This work showed that the LAAT could be used effectively by individuals, which is advantageous due to time constraints and the challenge of conducting MDT consensus meetings. The data also suggests that the Hallas scale (1990) is a suitable alternative tool to use depending on the study population; as witnessed from the ADRIC inpatient study, there were difficulties using Hallas due to the language used and the nature of prescribing (Thiesen et al. 2013).

The assessment of avoidability is complex and subjective which may lead to a degree of divergence which is unavoidable. The LAAT aims to minimise subjectivity by taking the reviewer through a series of questions but, it is impossible to eliminate subjectivity completely as reviewers may differ in their beliefs, experience and approach.

6.3 Future considerations - implications for research

ADRs form a large economic and social burden; the application of prevention strategies is thus of high importance. Clearly, more research is needed into interventions to help reduce the burden of ADRs in children. A thorough exploration of avoidable ADR cases could inform the development of practical interventions that can be translated into clinical practice. Key to this is the reduction of inappropriate or suboptimal prescribing and promotion of appropriate monitoring by: incorporating evidence-based updates to guidelines that specifically relate to the prevention and management of ADRs. Also there is a need to improve access to guidelines as seen in the consensus group meetings in Chapter 3; many clinicians had difficulty finding guidelines.

The three reasons for inconsistency suggest that there will always be an irreducible lack of consistency during the assessment of whether ADRs are avoidable and these factors need to be considered in the design of future studies. The development of other assessment tools, and further testing of the LAAT could be done in different ways.

This includes:

- Inclusion of an arm for unstructured assessment of cases in addition the existing approach
- A cross-over design between different approaches to assessment might also have been useful

- Interview people who were not in groups in order to get feedback on individual assessments
- Use of the LAAT by others outside the ADRIC group

In terms of improving the tool; external validation is the next logical step. External validation would ideally include the relevant experts from the different areas; so for example anaesthetists could be invited to review the ADR cases related to general anaesthetics; including the PONV cases. Consultant oncologists and Specialist oncology nurses and pharmacists could be invited to review ADRs related to chemotherapy. External validation could also be conducted using a panel of reviewers with experience and knowledge of ADRs for example members of the Paediatric Medicines Expert Advisory Group or Medical Assessors from the MHRA which would allow us to test the “utility” of the tool and identify if some of the observed difficulties were related to the tool or the types of reviewer.

Another possible study could involve asking reviewers to assess a set of cases for avoidability individually prior to attendance at a consensus meeting and to submit their assessments in advance of the meeting. The next step would involve attendance at a consensus meeting which would be chaired by an external moderator; to investigate if the results differed and whether there were examples of reviewers changing their minds. IRR testing could be conducted for both phases and results compared.

Assessing cases in “real time” and using case notes instead of case reports may give a more complete understanding of the situation and a greater awareness of contextual factors. For example, BP measurements should be available in “real time” assessments and therefore, may reduce the number of “unassessable” cases. Conducting prospective assessments using case notes may improve IRR. The rationale for using the ADRIC case reports in this work was that the LAAT was a tool

being validated to be used in paediatric inpatient avoidability assessments. Future work could include the assessment of ADRs prospectively using case notes.

6.3.1 Identification of potentially avoidable ADRs and strategies to reduce their incidence

Identification

One of the objectives of this thesis was to identify potentially avoidable ADRs and investigate ways to reduce their incidence. In terms of avoidability, constipation was the ADR most frequently categorised as avoidable. The reason for these cases being potentially avoidable was that no laxatives were given prophylactically. However, there is a lack of evidence in this area. The cases assessed with the LAAT were mainly classified as 'possibly avoidable' rather than 'definitely avoidable' as there is not always a guideline available. Other examples of potentially avoidable ADRs include immunosuppression, respiratory depression, vomiting and hypoglycaemia. Three key themes for avoidability have been established through a review of the existing literature (Jonville-Béra et al. 2009, Smyth et al. 2012, Gallagher et al. 2012, Temple et al. 2004) the themes are: inappropriate or suboptimal prescribing, medication administered to patient with history of ADR and Inadequate patient or parent education.

Table 5.4 in Chapter 5 indicates which therapeutic areas may be the most fruitful for future research including antibacterials, drugs used in diabetes, drugs used in status epilepticus and opioid analgesia. The predominant theme for avoidability was inappropriate or suboptimal prescribing in the case of the ADRs involving antibacterials there was a question over the indication for antibiotics given the evidence of viral illness. The majority of opioid related ADRs were constipation, in theory some of these ADRs might be avoidable with clearer guidance on the prevention of opioid related constipation and guidance on the co-prescribing of laxatives.

Potential strategies to avoid or reduce the incidence of ADRs

Gallagher et al. (2012) suggested some possible prevention strategies including improved monitoring, adherence to guidelines and patient education. From the assessment of the ADRs in this study the suggested strategies appear to fit with the data, further work needs to be done in this area to develop these strategies. Rashed et al. (2011) have suggested that knowledge of factors that predispose a patient to an ADR is important in the development of prevention strategies. They highlight the importance of improving the education of prescribers on identifying risk factors for ADRs and the concept of risk benefit assessments before prescribing medicines. This is similar to what is suggested by Pirmohamed and Ferner (2003) that educating prescribers and increasing patient's awareness is useful in the prevention of ADRs (Pirmohamed, Ferner 2003).

In adults, suggested prevention strategies include: the regular review of prescriptions, determining the clinical need for a particular medicine in a patient and using the lowest possible dose necessary to achieve benefit, the involvement of pharmacists in assessing prescribing behaviour and the use of electronic prescribing (Pirmohamed et al. 2008). Also, the work described in Chapters 3 and 4 have highlighted the need for improvement in the area of guidelines both in terms of accessibility and updates to include information that relates specifically to the prevention and management of ADRs.

Improving the practice of history taking and record keeping, educating patients and/or parents on their medicine's and raising awareness of ADRs amongst healthcare professionals are just a few examples of potential intervention strategies. The advances in technology and the use of Electronic prescribing (EP) and Clinical decision support systems (CDSS) could be targeted to help prevent ADRs occurring. Overall, CDSS have shown to reduce the numbers of ADEs (Routledge, O'Mahony & Woodhouse 2003, Wiffen et al. 2002). However, they also

introduce their own issues such as alert fatigue, sources of potential errors and rigidity of systems (Ash et al. 2007). EP has the potential to incorporate guidelines or clinical pathways making them more accessible to the prescribing clinician. These systems have the ability to prompt prescribers to consider co-prescribing prophylactic medicines in certain situations for example antiemetics in PONV or in oncology patients. By alerting clinicians to the potential risk of an ADR occurring and reminding them to consider appropriate laboratory monitoring (for example U&Es for ACE inhibitors) may help prevent ADRs from occurring in the first place or aid in the earlier detection of ADRs. However, whilst EP and CDSS have been shown to be beneficial they are not entirely perfect systems.

The advances in personalised medicines and pharmacogenomics may represent the ultimate method of avoidability. Pharmacogenomics aims to ultimately produce tailored medicines regimens based on a patient's genetic characteristics. Pharmacogenomic research in paediatric populations is ongoing but there are currently few clinical applications in paediatrics. However, there is considerable potential to improve the safety profile of medicines used in children (Hawcutt et al. 2013). The potential impact of personalisation of medicines, improving efficacy and reducing the side effects is an exciting area. An example of using pharmacogenomics to prevent ADRs in children is the treatment of acute lymphoblastic leukaemia (ALL). A pharmacogenetic test to determine the metabolism status of thiopurine methyltransferase has been incorporated into the treatment protocol (UKALL-2003). This allows patients who are found to be poor metabolisers to have their dose of 6-mercaptopurine amended to avoid any unwanted accumulation; thereby reducing the incidence of bone marrow toxicity. The changes to the guidance on the use of codeine have highlighted the importance of pharmacogenomics (Rieder, Carleton 2014).

Ototoxicity is a well-known ADR to cisplatin, but not all children who receive cisplatin will develop hearing loss. There is wide inter-patient variability even within standardised treatment regimens (Xu et al. 2015). There have been many studies to investigate cisplatin related ototoxicity and many potential candidate genes have been investigated but results have been inconsistent. The potential significance of identification of these genes could lead to interventions to reduce cisplatin related hearing loss and potentially aid in the development of less ototoxic therapies (Xu et al. 2015). Two genes which have been previously identified with known variants are thiopurine S-methyltransferase (TPMT) and catechol-O-methyltransferase (COMT). However there is conflicting evidence on their involvement. A paper published by Ross et al. (2009) reported a link between TPMT, COMT and ATP-binding cassette transporter C3 (ABCC3) variants and risk of ototoxicity. However, a contradictory article was published in 2013 where the authors concluded there was no link with genetic variation in COMT or TPMT and hearing loss related to cisplatin (Yang et al. 2013). Similarly no link was found by other researchers (Xu et al. 2015, Lanvers-Kaminsky et al. 2014).

Xu et al. (2015) conducted a genome-wide association study (GWAS) and identified common variants in ACYP2 which were associated with cisplatin related ototoxicity. The study involved 238 children with newly diagnosed brain tumours, they identified common variants in ACYP2 that were overrepresented in cisplatin-treated children who developed significant hearing loss. They conducted further testing on another 68 young children treated for brain tumours to validate their findings. They concluded further testing was needed in a larger cohort of patients but the clinical usefulness could be examined in future trials especially with a view to developing clinical interventions for at risk patients (Xu et al. 2015). Risk profiling children who are at increased risk of ADRs may help identify the most susceptible children and therefore identify where to focus efforts.

As mentioned earlier in Chapter 6, the addition of education sessions on the prevention and management of ADRs to undergraduate and postgraduate clinical training, or through the design of bespoke training packages may help to raise the awareness of ADRs among clinicians. A study conducted in Scotland in 2006 investigated the clinical pharmacology and therapeutics undergraduate training provided to first year foundation (FY1) programme doctors and whether or not this prepared doctors to prescribe safely. When asked specifically about ADRs 74% of participants reported having witnessed an ADR, of which approximately one third thought that the ADRs they had witnessed were both predictable and avoidable. Almost half of the participants felt that they had not received adequate training as an undergraduate about avoiding ADRs. The findings from this study highlighted the need to provide further training in ADRs, drug-drug interactions, contraindications and safe and rational use of medicines (Tobaiqy, M., McLay, J., & Ross, S 2007).

The Centre for Pharmacy Postgraduate Education (CPPE) launched an e-learning package (a three part series) on ADRs designed to help increase understanding and awareness of ADRs, their identification and prevention (CPPE 2014). In 2012 the BMJ and MHRA together launched an interactive e-learning module on pharmacovigilance free for all healthcare professionals in the UK. The aim of this training package was to provide guidance and support for healthcare professionals and to provide training on how and when to report ADRs (BMJ Learning 2012). In Liverpool a pilot study, randomised controlled trial (RCT) was conducted to test whether an e-learning tool which was developed to provide training in the use of the Liverpool causality assessment tool (LCAT) improved the ability of medical trainees to assign ADR causality using a series of reference ADR cases (Conroy et al. 2015).

Arnott et al. (2012) conducted a qualitative study with parents of children who had experienced a suspected ADR to gain some insight into their thoughts and experiences. Overall they found communication was poor and parents were generally disappointed with how clinicians communicated about suspected ADRs. Many parents reported receiving little or no information prior to starting a medicine about any potential ADRs which might occur. Consequently parents were often surprised when their child experienced a suspected ADR. Parents were concerned about their child experiencing ADRs in the future and what steps could be taken to prevent a reoccurrence. Parents appeared to undergo a similar process to clinicians establishing causality; they showed signs of linking their child's symptoms to the medicines prescribed. Interestingly, they found parents of children with cancer were generally highly satisfied with the level of communication provided by clinicians (Arnott et al. 2012). Improving patient and parent education by providing verbal counselling supported by written information about ADRs; this would inform patients about the potential for ADRs, advise them about what to look out for and what action to take if an ADR develops.

Arnott et al. (2012) indicated that parents would like to be better informed regarding their child's medicines and any potential side effects; perhaps by improving communication and involving parents in their child's treatment and alerting them to possible problems could potentially lead to a reduction in ADRs. Parents may be able to recognise ADRs and alert clinicians to their occurrence and in the case of previous suspected ADRs they can ensure this has been communicated to the clinical team and therefore help prevent the reoccurrence of and ADR where their child has a past history. Improved communication and documentation in patient records is a simple but effective method of ADR reduction. Examples of this were seen in Chapter 5, where a child had a past history of the same ADR which could have been potentially avoided on the second occasion with improved communication or documentation in the patient's notes.

Simple measures such as regular review of prescriptions, use of electronic prescribing, involvement of pharmacists in prescribing may all reduce ADRs (Davies et al. 2009). Prescribers should be vigilant for the occurrence of ADRs. The lowest possible dose and shortest duration of treatment should be considered. Patients should be monitored for ADRs to enable early detection. By involving parents more in their child's treatment and communicating the possibility of ADRs as suggested by Arnott et al (2012) may help with early detection of ADRs.

6.4 Conclusion

This thesis has shown that ADRs are a significant problem in children and that almost one fifth of them might be avoidable. Thus, 1 in 167 (0.6%) children admitted to hospital may have an avoidable ADR based on the figures from the ADRIC admissions study (Gallagher et al. 2012). It has highlighted the lack of reliable data available on ADRs and their prevention in children. In investigating the avoidability of ADRs, this thesis has contributed to the knowledge and highlighted the importance of further work being conducted in this area. This thesis has identified specific gaps in the literature and indicated key areas for future work.

The lack of common definitions (as discussed in Chapters 1 and 2) has caused problems in the past for comparison of studies and determining accurate avoidability rates (Hakkarainen et al. 2012a, Smyth et al. 2012). The introduction of common definitions would be a platform to do more. It would facilitate direct comparison of studies and enable a more accurate estimate of ADR avoidability rates in children. Educating and training of healthcare professionals at undergraduate and postgraduate levels and generally raising the awareness of ADRs promoting a culture within NHS and institutions could also potentially reduce the number of ADRs.

Although the LAAT was designed predominantly as a research tool it could possibly be used in other settings. It could potentially be used for organisational change by inviting members of the drug and therapeutic committee and senior clinicians with experience in the regulatory field to assess the avoidability of a selection of ADR case reports using the LAAT to help identify prevention strategies and inform change.

In summary, we have designed a novel avoidability assessment tool, developed by a MDT approach which has shown that it is comparable to an existing avoidability tool, can be used by individuals and most importantly is suitable for use in paediatrics or other areas where the clinical conditions extend beyond the expertise of individuals. A more in depth, expert-led review of ADRs and their prevention is required. The next step is to design interventions based on the findings in Chapter 5 (Table 5.4) as outlined in the discussion.

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Appendix 1 Sample ADR case



In Confidence



SUSPECTED ADVERSE DRUG REACTIONS

PATIENT DETAILS

Age (at time of admission): 3 yrs 4 m 10 d
Age (at time of reaction): 3 yrs 4 m 11 d

Sex: M Weight if known (kg): 11.2 kg

Identification number (ADRID.):

383

SUSPECTED DRUG(S)

Name	Route	Dose	Date Given	Frequency
fentanyl citrate[Given in theatre]	IV Infusion	10mcg+10mcg+10mcg	14/12/2009	
Morphine Sulphate[]	IV Infusion	11mg/50mls	14/12/2009	0.5ml/hr
Morphine Sulphate[]	IV Infusion	11mg/50mls	15/12/2009	0.5ml/hr
Nitrous oxide[Given in theatre]	Inhaled		14/12/2009	
propofol[Given in theatre]	IV Infusion	60mg	14/12/2009	1
sevoflurane[Given in theatre]	Inhaled		14/12/2009	

SUSPECTED REACTION(S)

ADR Type: Procedural vomiting

Specific treatment for ADR:

anti-emetic

Medical History

Fracture left radius and ulna

Admission Date: 14/12/2009 Discharge Date: 16/12/2009

Reason for Admission

Open reduction and internal Fixation of left arm

Case Summary:

Went to theatre on 14/12/09. Anaesthetic time approx. 90mins. Returned to ward 16:00.
On 15/12 am complained of feeling sick and vomited x1. Ondansetron given at 08:40 with good effect. Morphine stopped at 14:00 same day. Fluids and diet tolerated after this and no further reports of nausea/vomiting.

Date reaction(s) started: 15/12/2009

Date reaction(s) stopped: 15/12/2009

Duration of ADR: 1 Days

Do you consider the reaction to be serious?: No, not serious

Severity: Required treatment, or drug administration discontinued

Outcome: Recovered

Action Taken With Drugs: Not applicable

Did the patient need a higher level of care due to ADR? No

Discussed with clinician? No

Was the patients stay prolonged due to ADR: No

Discussed with clinician? No

OTHER DRUGS

Name	Route	Dose	Freq	Date Given
cefuroxime	IV Infusion	250mg	1	14/12/2009
cefuroxime	IV Infusion	250mg	1	15/12/2009
Diclofenac	Oral	12mg	1	14/12/2009
Diclofenac	Oral	12mg	1	15/12/2009
ondansetron hydrochloride	IV inj	1.2mg	1	15/12/2009
paracetamol	Oral	220mg	1	14/12/2009
paracetamol	Oral	220mg	3	15/12/2009
paracetamol	Oral	220mg	2	16/12/2009
Codeine Phosphate	Oral	10mg	1	15/12/2009
Codeine Phosphate	Oral	10mg	2	16/12/2009

Reporter Details

This report was completed as part of the ADRIC Programme.

Should you require any further information please contact:

Helen Mansly Research Nurse

Identification number (ADRID.):

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Appendix 2 Avoidability tool glossary – Liverpool ADR avoidability assessment tool glossary

- **Known preventative strategies:** prophylactic or concomitant medicines or any necessary monitoring.
- **Appropriate management plan(s):** a plan that would be recognised as appropriate by a reasonable body of opinion. This could refer to **any** local, national or international guideline that could be available to the prescriber e.g. hospital guidelines, National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), British thoracic society (BTS), the British society for paediatric and adolescent rheumatology (BSPAR) or World health organisation (WHO).

For example in the case of post-operative nausea and vomiting; examples of appropriate management plans could include: Alder Hey Children's NHS Trust guideline on post-operative nausea and vomiting or the association of paediatric anaesthetists of Great Britain and Ireland (APA) guideline on the prevention of post-operative vomiting in children.

- **Information about the ADR and its avoidance:** does the management plan mention any preventative measures to be taken to avoid the ADR including medicines to be given prophylactically or concomitantly or any necessary monitoring etc. (electrolytes, FBC or BP)? A management plan may or may not contain information regarding prevention of ADRs but more often than not they contain no information regarding the prevention of ADRs.
- **Other information sources:** examples include the BNFC (British National Formulary for children), SmPC (Summary of Product Characteristics), advice from colleagues, history from the parents/patients or information from a journal article etc. (if the prescriber could reasonably be expected to use these sources)
- **Unassessable:** the case could not be assessed due to lack of information about the case and/or treatment; or due to conflicting information.
- **Not avoidable:** the ADR was unavoidable based on the information available at the time of the reaction. There are four scenarios which lead to an ADR being categorised as “not avoidable”
 1. If the reaction was unpredictable and there was no known history of previous similar reaction or allergy to the drug.
 2. If there was an appropriate management plan with information about the ADR and its avoidance and it was followed.
 3. If there was no appropriate management plan, with information about the ADR and its avoidance available, there were no other information sources available to consult and there was no information in the history available for prevention of the ADR.
 4. If there was no appropriate management plan, with information about the ADR and its avoidance available but there were other information sources available to consult or information in the history available for prevention of the ADR and appropriate action was taken to avoid the ADR.
- **Possibly avoidable:** there was no appropriate management plan available to follow but there were other information sources or information in the history available to prevent the ADR and these were not followed.
- **Definitely avoidable:** there were known preventative strategies or an appropriate management plan was available with information about the avoidance of the ADR but the strategies and or management plan were not followed.

Guide to questions in the avoidability tool

Is there sufficient information available about the case and the treatment to allow assessment?

If the answer is 'yes' there is sufficient information available about the case and the treatment then the assessor can proceed to the next question if the answer is 'no' either due to lack of information or conflicting information the case becomes 'unassessable' (this category may not be assigned until the case has been reviewed and guideline/information sought).

Was the reaction predictable on the basis of the known pharmacology of the drug(s)?

This question relates to whether the ADR is predictable on the basis of known pharmacology as there is lots of 'unknown' pharmacology. If the answer is 'no' then you proceed to the question asking if there was a known history of a previous similar reaction. If the answer is 'yes' then you proceed down the left hand side of the flow diagram where you are asked questions regarding availability of appropriate management plans and if they were followed.

Was there a known history of allergy or previous similar reaction to the drug?

The purpose of this question is to establish if the patient has experienced a similar reaction in the past and by answering 'no' to the question takes you to 'not avoidable' as for unpredictable reactions where the patient has no previous history of it occurring the reaction could not have been prevented on this occasion. In theory this reaction could be avoided in the future.

Were other information sources, or information in the history available for prevention of the ADR which could have been followed?

This is an important question to establish if there was something else which could have been done to avoid the ADR either by consulting a more senior clinician for advice or looking in another reference source; examples include but are not limited to BNFC (British National Formulary for children), SmPC (Summary of Product Characteristics), consulting the parents or conducting a quick search for journal article etc. if the answer is 'no' to this question then the reaction is categorised as 'not avoidable' if the answer is 'yes' you proceed to the next question.

Was appropriate action taken to avoid the ADR?

This question allows the reaction to be categorised as 'not avoidable' if appropriate action was taken to avoid the ADR but it occurred anyway and for cases where other information sources were available but the appropriate action was not taken i.e. answering 'no' to the question categorises the ADR as 'possibly avoidable'.

Were there known preventative strategies and/or appropriate management plan(s), with information about the ADR and its avoidance, available?

This question is designed to establish if there was an appropriate treatment guideline available. This could include **any** local, national or international guideline available to the clinical team when the child was seen e.g. hospital guidelines, NICE (National Institute for Health and Clinical Excellence), SIGN (Scottish Intercollegiate Guidelines Network), BTS (British thoracic society), WHO (World health organisation). If there was information available on the management of the condition but the guidance makes no reference to the ADR or its prevention then by answering 'no' to the question you are directed to answer the question about whether other information sources were available. This allows for the application of other measures. If the answer is 'yes' to this question you proceed to the next question below.

Were the strategies and/or management plan(s) followed?

If there was an appropriate management plan available and it contained information about the avoidance of the ADR but it was not followed this would mean by answering 'no' to this question categorises the ADR as 'definitely avoidable' if the answer is 'yes' the drug(s) was used in accordance with the management plan then the ADR is categorised as 'not avoidable'.

Appendix 3 Sample participant information sheets and a copy of the consent form



Version 1.2 17/10/13

Participant Information Sheet: The Development and Testing of the Liverpool Adverse Drug Reaction Avoidability Assessment Tool

Thank you for taking time to read this information sheet. You are being invited to take part in a research study. Please ask us if there is anything that is not clear in this information sheet or if you would like more information.

Why are we doing this study?

The aim of this study is to test a new way of determining whether adverse drug reactions are avoidable. The Liverpool avoidability assessment tool (LAAT) was developed through the Adverse Drug Reactions in Children (ADRIC) research programme.

Why have I been invited?

You have been invited to participate because you are a clinician (nurse, pharmacist, doctor) working at Alder Hey Children's NHS Foundation Trust.

Do I have to take part?

No it is your decision entirely. If you decide to take part, you will be given this information sheet to keep and will be asked to sign a consent form. You are still free to withdraw from the study at any time and without giving a reason.

What will taking part involve?

If you have agreed to take part you will be assigned to either one of the three consensus groups (A/B/C) or to the individual assessment group (where reviewers will independently assess the cases). Each consensus group will be made up of a multidisciplinary team (nurse, pharmacist, doctor). You will either be required to attend a consensus group meeting or to assess the same set of case reports individually.

The consensus meetings will last approximately 2-2.5 hours; during which the group will be asked to look through a series of 15 – 20 case reports of adverse drug reactions. The group will be asked to use the LAAT to decide whether each adverse drug reaction was avoidable or not. The meetings will be audio-recorded and transcribed but all identifiable details will be removed or anonymised.

All participants will also be invited to take part in short interviews (15-20 minutes) after the consensus meetings have taken place. The purpose of the interviews is to explore reviewers' accounts of the consensus meetings. The interviews will be conducted by Louise Bracken who will ask you about your experiences of the consensus meetings and how useful you found it. If there are any questions you do not want to answer just tell the interviewer and she will move to the next topic. You can also stop the interview at any point.

With your agreement we would like to audio-record the interviews. We will transcribe the interviews and anonymise them by removing all identifying details.

Do I have to take part?

No – it is your decision entirely. If you decide to take part, you will be given this information sheet to keep and will be asked to sign a consent form. You are still free to withdraw from the study at any time and without giving a reason.

If I am assigned to a consensus group do I have to take part in the post-meeting interviews?

No –it is your decision entirely. You can choose to only take part in the consensus meetings. If you decide to take part

How long will it take?

We estimate that the consensus group meetings will no more than 2-2.5 hours. There will also be an optional debrief session lasting 20 minutes at the end of the meeting. We estimate that the individual assessment of the ADR case reports will also take no more than 2.5 hours.

What are the benefits of taking part?

By taking part, you will help us to assess the utility of the LAAT and if it is useful, the best way use the tool. You will have the opportunity to undertake some structured assessments of a series of ADR cases which have relevance to paediatric practice. If you would like some feedback about the assessment of ADRs in children this will be available during the optional debrief.

How will the data collected about me be stored and used?

All data collected for this study will be kept safely and securely on computer and on transcribed paper records. Dr Mark Turner will be the custodian of all study data. With your permission, study records will be archived and stored at Alder Hey Children's Hospital NHS Foundation Trust for up to 5 years after the end of this study for research review purposes. If you do not wish your records to be stored they will be destroyed at the end of the current study.

After all identifying details have been removed from the transcribed records of audio-recordings, these will be analysed by the study team. The results will be published in reports and scientific journals, but it will not be possible to identify any individuals from these reports. We will send you a summary of the results at the end of the study if you would like one.

What should I do if I am unhappy about the research at any time? If you are unhappy, or if there is a problem, please contact Dr Mark Turner by email at mark.turner@liverpool.ac.uk and he will try to help. If you remain unhappy or have a complaint which you feel you cannot bring to us, then you should contact the Research Governance Officer on 0151 794 8290 (ethics@liv.ac.uk).

Who can I contact for further information?

You can contact Louise Bracken by email at louise.bracken@alderhey.nhs.uk or by phone at 0151 236 4751 or alternatively, Dr Mark Turner by email at mark.turner@liverpool.ac.uk or by phone at 0151 795 9558.

PARTICIPANT CONSENT FORM (version 1.2 17/10/13)

Title of Research Project:

The development and testing of the Liverpool adverse drug reaction avoidability assessment tool

Researcher(s):

Please
initial
box

1. I confirm that I have read and have understood the information sheet dated 17/10/13 (version 1.2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my rights being affected.

3. I understand that the group consensus meetings will be audio-recorded and transcribed and I am aware of and consent to your use of these recordings for the following purposes: brief quotations from the meetings may be included in study reports. I understand that nobody will be able to identify any participants in these reports.

4. I agree to study records (including transcripts of the consensus meetings and interviews) being stored at Alder Hey Children's NHS Trust after the end of this study. I understand that these will be held securely and marked with a number only.

5. I understand that, under the Data Protection Act, I can at any time ask for access to the information I provide and I can also request the destruction of that information if I wish.

6. I understand that if I am assigned to the consensus group and agree to take part in a post-meeting interview that it will be audio-recorded and transcribed and that brief quotations from some interviews may be included in study reports. I understand that nobody will be able to identify any participants in these reports

7. I agree to take part in the above study.

Participant Name

Date

Signature

Name of Investigator

Date

Signature

Supervisor:

Name: Dr Mark Turner
Work Address: Liverpool Women's Hospital
Work telephone: 0151 795 9558
Work email: mark.turner@liverpool.ac.uk

Student Researcher:

Name: Louise Bracken
Work Address: Alder Hey Children's Hospital
Work telephone: 0151 282 4751
Work email: louise.bracken@alderhey.nhs.uk

Appendix 4 Feedback Survey- Testing of the Liverpool ADR avoidability assessment tool (LAAT)

Please circle your answers.

What is your role?

1. Nurse
2. Doctor
3. Pharmacist

	Strongly Agree	Agree	Undecided	Disagree	Strongly Disagree
=====					
1. The LAAT was easy to use.	1	2	3	4	5
2. Some questions were harder to answer.	1	2	3	4	5
3. I would have been able to answer all the questions by myself ? (n/a to individual assessors please skip to question 4)	1	2	3	4	5
4. It may have been easier to assess the cases in a group setting. (n/a to those involved in consensus groups please skip to question 5).	1	2	3	4	5
5. The tool could potentially have some utility in the future .	1	2	3	4	5

6. If you have any additional comments to add please write them in the box below.

Thank you for taking part in the study and for completing the feedback survey your contribution is much appreciated.

Appendix 5 Results from the Likert scales- individuals and groups

Results from the Individuals

	Strongly Agree	Agree	Undecided	Disagree	Strongly Disagree
Doctor 1					
The LAAT was easy to use.		x			
I found some questions harder to answer (for some questions it was difficult to decide between a positive and negative response)	x				
In some cases it was difficult to judge whether guidelines or information were available		x			
It may have been easier to assess the cases in a group setting				x	
The tool could potentially have some utility in the future	x				
Additional comments: none					
Doctor 2					
The LAAT was easy to use.				x	
I found some questions harder to answer (for some questions it was difficult to decide between a positive and negative response)		x			
In some cases it was difficult to judge whether guidelines or information were available		x			
It may have been easier to assess the cases in a group setting		x			
The tool could potentially have some utility in the future			x		
Additional comments: Not always easy to judge if other sources of info are available					
Doctor 3					
The LAAT was easy to use.		x			
I found some questions harder to answer (for some questions it was difficult to decide between a positive and negative response)		x			
In some cases it was difficult to judge whether guidelines or information were available		x			
It may have been easier to assess the cases in a group setting			x		
	x				

Results from the Individuals (continued)

	Strongly Agree	Agree	Undecided	Disagree	Strongly Disagree
Additional comments: none					
Nurse 1					
The LAAT was easy to use.		x			
I found some questions harder to answer (for some questions it was difficult to decide between a positive and negative response)		x			
In some cases it was difficult to judge whether guidelines or information were available	x				
It may have been easier to assess the cases in a group setting	x				
The tool could potentially have some utility in the future		x			
Additional comments: none					
Nurse 2					
The LAAT was easy to use.		x			
I found some questions harder to answer (for some questions it was difficult to decide between a positive and negative response)		x			
The tool could potentially have some utility in the future	x				
It may have been easier to assess the cases in a group setting			x		
The tool could potentially have some utility in the future	x				
Additional comments: none					
Nurse 3					
The LAAT was easy to use.		x			
I found some questions harder to answer (for some questions it was difficult to decide between a positive and negative response)	x				
In some cases it was difficult to judge whether guidelines or information were available			x		
It may have been easier to assess the cases in a group setting	x				
The tool could potentially have some utility in the future	x				
Additional comments: I had to use BNFC, nurse's dictionary & google for clarification of drugs and conditions					
Pharmacist 1					
The LAAT was easy to use.			x		

Results from the Individuals (continued)

	Strongly Agree	Agree	Undecided	Disagree	Strongly Disagree
I found some questions harder to answer (for some questions it was difficult to decide between a positive and negative response)		x			
In some cases it was difficult to judge whether guidelines or information were available		x			
It may have been easier to assess the cases in a group setting	x				
The tool could potentially have some utility in the future		x			
Additional comments: none					

Pharmacist 2

The LAAT was easy to use.	x				
I found some questions harder to answer (for some questions it was difficult to decide between a positive and negative response)		x			
In some cases it was difficult to judge whether guidelines or information were available		x			
It may have been easier to assess the cases in a group setting				x	
The tool could potentially have some utility in the future	x				
Additional comments: none					

Pharmacist 3

The LAAT was easy to use.	x				
I found some questions harder to answer (for some questions it was difficult to decide between a positive and negative response)				x	
In some cases it was difficult to judge whether guidelines or information were available				x	
It may have been easier to assess the cases in a group setting			x		
The tool could potentially have some utility in the future		x			

Result from the Likert scale – Consensus groups

	Strongly Agree	Agree	Undecided	Disagree	Strongly Disagree
Pharmacist 04/02					
The LAAT was easy to use		x			
I found some questions harder to answer (for some questions it was difficult to decide between a positive and negative response)	x				
In some cases it was difficult to judge whether guidelines or information were available		x			
I would have been able to answer all the questions by myself		x			
The tool could potentially have some utility in the future		x			
Other comments: Sometimes difficult to assess if a 'management plan' was adhered to!					
Pharmacist 10/02					
The LAAT was easy to use		x			
I found some questions harder to answer (for some questions it was difficult to decide between a positive and negative response)		x			
In some cases it was difficult to judge whether guidelines or information were available		x			
I would have been able to answer all the questions by myself			x		
The tool could potentially have some utility in the future	x				
Other comments: none					
Pharmacist 26/02					
The LAAT was easy to use			x		
I found some questions harder to answer (for some questions it was difficult to decide between a positive and negative response)		x			
In some cases it was difficult to judge whether guidelines or information were available		x			
I would have been able to answer all the questions by myself				x	
The tool could potentially have some utility in the future			x		
Other comments: Perhaps the tool would have future potential value with modification to include consideration of ADR and deliberate decision to proceed in a certain cause of action.					
Nurse 04/02					
The LAAT was easy to use		x			
I found some questions harder to answer (for some questions it was difficult to decide between a positive and negative response)	x				
In some cases it was difficult to judge whether guidelines or information were available		x			
I would have been able to answer all the questions by myself			x		
The tool could potentially have some utility in the future		x			
Other comments: none					
Nurse 10/02					
The LAAT was easy to use		x			

Results from the Groups (continued)	Strongly Agree	Agree	Undecided	Disagree	Strongly Disagree
In some cases it was difficult to judge whether guidelines or information were available		x			
I would have been able to answer all the questions by myself			x		
The tool could potentially have some utility in the future	x				
Other comments: none					
Nurse 26/02					
The LAAT was easy to use			x		
I found some questions harder to answer (for some questions it was difficult to decide between a positive and negative response)		x			
In some cases it was difficult to judge whether guidelines or information were available		x			
I would have been able to answer all the questions by myself				x	
The tool could potentially have some utility in the future		x			
Other comments: with some ADRs it was difficult to decide as there could be more than one route.					
Doctor 04/02					
The LAAT was easy to use		x			
I found some questions harder to answer (for some questions it was difficult to decide between a positive and negative response)		x			
In some cases it was difficult to judge whether guidelines or information were available		x			
I would have been able to answer all the questions by myself		x			
The tool could potentially have some utility in the future	x				
Other comments: Useful tool					
Doctor 10/02					
The LAAT was easy to use		x			
I found some questions harder to answer (for some questions it was difficult to decide between a positive and negative response)		x			
In some cases it was difficult to judge whether guidelines or information were available				x	
I would have been able to answer all the questions by myself				x	
The tool could potentially have some utility in the future		x			
Other comments: none					
Doctor 26/02					
The LAAT was easy to use		x			
I found some questions harder to answer (for some questions it was difficult to decide between a positive and negative response)	x				
In some cases it was difficult to judge whether guidelines or information were available	x				
I would have been able to answer all the questions by myself			x		
The tool could potentially have some utility in the future	x				
Other comments: Was appropriate action taken box- should include addendum to detail that side effect/ADR was considered but that benefit to patient outweighed risk. Were there known preventative strategies box should include footnote to list considerable guidance e.g. protocols/NICE guidance/Journal					

Appendix 6 Interview topic guide

1. General professional background

- Role
- Grade
- How long since registration?
- How long have you been working in paediatrics?
- Any specialty?

2. Could you describe what you understand by avoidability of ADRs?

3. What is your understanding of an ADR?

- Could you describe an ADR? (prompt question could be how do you think ADRs are different from Adverse drug events or errors?)

May not need to ask next question depending on answer to question 3

What is your experience of ADRs in children?

- Prompt question: could you give me a general example of an ADR?

4. What is your first impression of the LAAT after using it (today/yesterday etc.)?

5. How did you find being part of a group?

6. Were there any advantages of being in a group, if yes what were these?

7. Were there any disadvantages of being in a group, if yes what were these?

8. Do you think you would have reached the same conclusions on your own?

9. Would you feel confident doing the ADR assessments on your own?

10. How do you think the tool could be used in the future?

11. Is there anything we haven't spoken about in the interview that you'd like to add?

Other useful questions if want more information: can you expand on that please?

Appendix 7 Coding Framework

Broad themes for qualitative analysis

Conceptual awareness

- Terminology
- Use and application of terms such as errors/ADEs/ADRs
- Use and application of terms such as avoidability, prevention, risk etc.

Clinical knowledge

- Knowledge and experience of ADRs
- Examples of ADRs
- Any reference to specific medicines, ADRs, ADEs etc.

Perceptions of groups versus individuals

- Perceived values of groups
- Confidence/reassurance
- Areas of expertise/specialty
- Advantages/disadvantages
- Power
- MDT
- Information sources

Perceptions of the tool

- Ease of use
- Initial impression
- Possible applications

Engagement with the tool

- Evidence of engagement with the tool e.g. through unprompted reference to aspects of the tool; giving examples of application or perceived value or future use of the tool; ability to converse with the researcher about the tool and demonstrate an awareness key aspects of the tool.
- Compare characteristics seniority/ profession etc.

Coding framework
Participants' data analysis

Participants

Nurses (n=3)

Doctors (n=3)

Pharmacists (n=2)

Initial/open coding	Emerging themes	Final coding and themes
Participant's knowledge about ADRs/clinical knowledge	<ul style="list-style-type: none"> • Drawing on own knowledge and experience of ADRs • Refer back to examples of ADRs • Makes references to specific medicines • Clinicians don't always use guidelines. Guidelines - using them/finding them 	<p>Rely on own tacit knowledge. Reluctant to search for and use existing guidelines.</p> <p>Rely on personal previous experience of ADRs.</p> <p>Perceptions rooted in personal clinical experience.</p>
Awareness and familiarity with terminology Conceptual awareness	<ul style="list-style-type: none"> • Interchangeable use and application of terms such as errors/ADEs • Interchangeable use and application of terms such as avoidability, prevention and risk 	Confusion about terminology.
Groups/MDT appreciation of other members expertise and contribution to the process	<ul style="list-style-type: none"> • Perceived values of groups • Confidence/reassurance • Dependency • Areas of expertise/specialty • Advantages/disadvantages • Power • MDT • Judgement – appraising judgement • Information sources 	<p>Perceptions of groups versus individuals.</p> <p>Clinicians were generally positive about assessing cases within a group and could see a number of advantages to working within an MDT.</p> <p>Clinicians especially valued access to expertise.</p> <p>They felt working as an MDT speeded up decision making and promoted more balanced decisions.</p> <p>Reduced feelings of blame and judgement.</p>
How clinicians perceive the tool	<ul style="list-style-type: none"> • Ease of use • Initial impression • Possible applications • Context specific 	<p>Perceptions of the tool.</p> <p>Clinicians were generally positive about the tool and could see how it could be used in practice.</p> <p>One clinician commented that the tool could promote self-reflective practice.</p>
How clinicians engaged with the tool	<ul style="list-style-type: none"> • Future use and perceived value • Compare characteristics seniority/profession etc. 	Engagement with the tool

Appendix 8 Final version of the Liverpool ADR avoidability assessment tool glossary

- **Known preventative strategies:** prophylactic or concomitant medicines or any necessary monitoring.
- **Appropriate management plan(s):** a plan that would be recognised as appropriate by a reasonable body of opinion. This could refer to **any** local, national or international guideline that could be available to the prescriber e.g. hospital guidelines, National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), British thoracic society (BTS), the British society for paediatric and adolescent rheumatology (BSPAR) or World health organisation (WHO) or a 'personalised management plan'.

For example in the case of post-operative nausea and vomiting; examples of appropriate management plans could include: Alder Hey Children's NHS Trust guideline on post-operative nausea and vomiting or the association of paediatric anaesthetists of Great Britain and Ireland (APA) guideline on the prevention of post-operative vomiting in children.
- **Information about the ADR and its avoidance:** does the management plan mention any preventative measures to be taken to avoid the ADR including medicines to be given prophylactically or concomitantly or any necessary monitoring etc. (electrolytes, FBC or BP)? A management plan may or may not contain information regarding prevention of ADRs but more often than not they contain no information regarding the prevention of ADRs.
- **Other information sources:** examples include the BNFC (British National Formulary for children), SmPC (Summary of Product Characteristics), advice from colleagues, history from the parents/patients or information from a journal article etc. (if the prescriber could reasonably be expected to use these sources)
- **Unassessable:** the case could not be assessed due to lack of information about the case and/or treatment; or due to conflicting information.
- **Not avoidable:** the ADR was unavoidable based on the information available at the time of the reaction. There are four scenarios which lead to an ADR being categorised as "not avoidable"
 1. If the reaction was unpredictable and there was no known history of previous similar reaction or allergy to the drug.
 2. If there was an appropriate management plan with information about the ADR and its avoidance and it was followed.
 3. If there was no appropriate management plan, with information about the ADR and its avoidance available, there were no other information sources available to consult and there was no information in the history available for prevention of the ADR.

4. If there was no appropriate management plan, with information about the ADR and its avoidance available but there were other information sources available to consult or information in the history available for prevention of the ADR and appropriate action was taken to avoid the ADR.
- **Possibly avoidable:** there was no appropriate management plan available to follow but there were other information sources or information in the history available to prevent the ADR and these were not followed.
 - **Definitely avoidable:** there were known preventative strategies or an appropriate management plan was available with information about the avoidance of the ADR but the strategies and or management plan were not followed.

Guide to questions in the avoidability tool

Is there sufficient information available about the case and the treatment to allow assessment?

If the answer is 'yes' there is sufficient information available about the case and the treatment then the assessor can proceed to the next question if the answer is 'no' either due to lack of information or conflicting information the case becomes 'unassessable' (this category may not be assigned until the case has been reviewed and guideline/information sought).

Was the reaction predictable on the basis of the known pharmacology of the drug(s)?

This question relates to whether the ADR is predictable on the basis of known pharmacology as there is lots of 'unknown' pharmacology. If the answer is 'no' then you proceed to the question asking if there was a known history of a previous similar reaction. If the answer is 'yes' then you proceed down the left hand side of the flow diagram where you are asked questions regarding availability of appropriate management plans and if they were followed.

Was there a known history of allergy or previous similar reaction to the drug?

The purpose of this question is to establish if the patient has experienced a similar reaction in the past and by answering 'no' to the question takes you to 'not avoidable' as for unpredictable reactions where the patient has no previous history of it occurring the reaction could not have been prevented on this occasion. In theory this reaction could be avoided in the future.

Were other information sources, or information in the history available for prevention of the ADR which could have been followed?

This is an important question to establish if there was something else which could have been done to avoid the ADR either by consulting a more senior clinician for advice or looking in another reference source; examples include but are not limited to BNFC (British National Formulary for children), SmPC (Summary of Product Characteristics), consulting the parents or conducting a quick search for journal article etc. if the answer is 'no'

to this question then the reaction is categorised as 'not avoidable' if the answer is 'yes' you proceed to the next question.

Was appropriate action taken to avoid the ADR?

This question allows the reaction to be categorised as 'not avoidable' if appropriate action was taken to avoid the ADR but it occurred anyway and for cases where other information sources were available but the appropriate action was not taken i.e. answering 'no' to the question categorises the ADR as 'possibly avoidable'.

Were there known preventative strategies and/or appropriate management plan(s), with information about the ADR and its avoidance, available?

This question is designed to establish if there was an appropriate treatment guideline available. This could include **any** local, national or international guideline available to the clinical team when the child was seen e.g. hospital guidelines, NICE (National Institute for Health and Clinical Excellence), SIGN (Scottish Intercollegiate Guidelines Network), BTS (British thoracic society), WHO (World health organisation). If there was information available on the management of the condition but the guidance makes no reference to the ADR or its prevention then by answering 'no' to the question you are directed to answer the question about whether other information sources were available. This allows for the application of other measures. If the answer is 'yes' to this question you proceed to the next question below.

Were the strategies and/or management plan(s) followed?

If there was an appropriate management plan available and it contained information about the avoidance of the ADR but it was not followed this would mean by answering 'no' to this question categorises the ADR as 'definitely avoidable' if the answer is 'yes' the drug(s) was used in accordance with the management plan then the ADR is categorised as 'not avoidable'.